AUS DEM LEHRSTUHL
FÜR DERMATOLOGIE
PROF. DR. MED. DR. H. C. M. LANDTHALER
DER FAKULTÄT FÜR MEDIZIN
DER UNIVERSITÄT REGENSBURG

IDENTIFICATION OF NEW GENES ASSOCIATED WITH MELANOMA

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

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Fakultät für Medizin
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Identification of new genes associated with melanoma

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Abbreviations:

PM: primary melanoma

MM: melanoma metastases

MN: melanocytic nevi

GDF15: growth differentiation factor 15

TLE1: transducin-like enhancer of split 1 (E(sp) homolog, Drosophila)

CNTN1: contactin 1

FRZB: frizzled-related protein

MMP1: matrix metalloproteinase 1

ALM: acral lentiginous melanoma

LMM: lentigo maligna melanoma

SSM: superficial spreading melanoma

NMM: nodular melanoma

FFPE: formalin-fixed, paraffin-embedded

PFS: progression free survival

Abstract:

Purpose: Repeated failures in melanoma therapy made clear that the molecular mechanisms leading to melanoma are still poorly understood. Here, we aim to provide a more comprehensive understanding of the transcriptional profiles and signaling pathways associated with melanoma.

Methods: Gene expression was analyzed using the Affymetrix Human Genome U133A 2.0 GeneChip arrays. To avoid culture artifacts, we used microdissected fresh frozen material of 18 melanocytic nevi (MN), 20 primary melanomas (PM) and 20 metastatic melanomas (MM). Statistical analysis was performed with Genomatix Chipinspector, Ingenuity™ Software, SPSS Software and Partek Genomic Suite 6.4. Expression levels of selected transcripts were verified by quantitative real-time RT-PCR and immunostaining of a tissue microarray sampling more than 280 cases of MN, PM, and MM with known clinical outcome.

Results: A total of 284 differentially expressed genes was detected in PM compared to MN and 189 genes in MM compared to PM affecting common cancer pathways such as MAPK-, Wnt-, and Notch-signaling. Using principal component analysis, the samples could be grouped according to their histological entity. We identified a panel of novel melanoma-associated markers: FRZB, an antagonist of Wnt; TLE1, a transcription factor partner of TCF/LEF-1; CNTN1, an activator of Notch signaling; two Serpin peptidase inhibitors, Serpin B3/B4, and the TGF-β family member GDF15, the latter with association to MAPK-signaling.

Key words:

Melanoma, FRZB, TLE1, Serpin B3, Serpin B4

Introduction

Melanoma is increasing in incidence with 68,130 cases expected for 2010 in the United States and an annual death rate of 4.07 per 100,000, corresponding to a total of 8700 estimated deaths [1]. Melanoma patients with a tumor thickness of < 1mm have a favorable cure rate but once melanoma has progressed into systemic disease, median survival drops below 7-8 months and the 5 year survival is less than 5% [2]. Since cellular homeostasis in melanoma is deregulated by a concert of genes [3], it is important to develop new diagnostic and therapeutic strategies taking into account the entire tumor signature rather than one single marker. To gain insights into genome-wide gene expression patterns in cancer, microarray technology became a powerful instrument and the recent progress in computational analysis allows investigating whole networks of signaling pathways in individual patient samples at the same time. Since single pathways, e.g. MAPK signaling, have been targeted so far only with limited success [4], a better understanding of the entire spectrum of signaling networks and there interconnection is highly needed for the design of future therapies [5].

Although applied for years now, the benefit of microarrays for melanoma research is still limited, because the majority of studies has been based on cultured cell lines. Certainly, experimental conditions can be stably controlled in cell culture, but on the downside, gene expression is affected by the selected culture media leading to artifacts in the results. Among the few studies that have analyzed in vivo patient samples, e.g. Jaeger et al. [6] compared gene expression patterns of 19 primary melanomas (PM) and 22 melanoma metastases (MM). Their results showed that PM and MM were characterized by distinct gene expression patterns and represent different biological stages of tumor progression. However, since benign nevi (MN) were not included, an interpretation with regard to initial malignant processes was not possible. A former study of our group on a limited number of laser-microdissected patient samples, indicated that particularly the comparison to MN could reveal significant changes in the transcriptional profiles of PM [7].

Here, we aim to detect new gene expression alterations in PM and MM compared to MN, which may contribute to tumor initiation and progression of this deadly disease. We applied high throughput transcriptional profiling followed by network analysis to a large number of fresh frozen patient specimens of MN, PM and MM and subsequently performed validation experiments to a panel of significantly regulated and promising new candidate genes.

Methods

Patient Material

For microarray analysis, tissue samples from 18 MN, 20 PM (2 acral lentiginous melanomas, 3 lentigo maligna melanomas, 4 nodular melanomas, 5 secondary nodular melanomas, and 6 superficial spreading melanomas) and 20 MM (cutaneous and lymph node metastases) were collected at the Department of Dermatology, University of Regensburg, Germany (Table 1). Patients' written consent was obtained prior to surgery. The tissue specimens were immediately frozen in liquid nitrogen and stored at –80°C. Histological diagnoses were routinely assessed by two expert dermatopathologists (M.L. and T.V.) prior to RNA extraction.

RNA Isolation and microarray hybridization

RNA was extracted using QIAshredder columns (Quiagen, Hilden, Germany) and the RNeasy Mini Kit (Quiagen) as previously described [8]. RNA quality control was done with an Agilent Bioanalyzer 2100 (Agilent Technologies, Palo Alto, USA). 1 to 5 micrograms of total RNA from each tissue specimen were used to generate double-stranded cDNA and biotin-labeled cRNA (One Cycle Target Labeling Kit, Affymetrix). The length of the cRNA products was assessed using the Agilent 2100 bioanalyzer (Agilent Technologies, Palo Alto, USA). Following fragmentation, cRNA products (10 µg) were hybridized to Affymetrix Human Genome U133A 2.0 GeneChip® (Affymetrix, Santa Clara, USA) arrays for 16 h at 45° C in a rotating chamber. The array contained about 22,000 probe sets representing 14,500 human genes. Hybridized arrays were washed and stained in Affymetrix Washing Station FS400 using Streptavidin Phycoerythrin conjugate (Molecular Probes, Eugene, USA) together with biotinylated anti-streptavidin antibody (Vector Laboratories, Burlingame, USA), and the fluorescent signals were measured with the Affymetrix GeneChip® Scanner 3000. Quality control of the isolated RNA samples and sample processing were performed at a regional German Affymetrix Service Provider and Core Facility, "KFB - Center of Excellence for Fluorescent Bioanalytics" (www.kfb-regensburg.de).

Tissue microarrays and Immunohistochemistry

Tissue microarrays were constructed as described previously [9] and contained formalin-fixed, paraffin-embedded (FFPE) human tissue samples of 127 MN, 73 PM, and 89 MM. The University of Regensburg institutional review board granted approval for the project. In brief, tissues were deparaffinized and rehydrated, according to standard protocols and subsequently incubated with a 1:600 dilution of anti-GDF15 polyclonal antibody (Abcam, Cambridge, UK) and a 1:2000 dilution of mouse anti-MMP1 monoclonal antibody (Millipore Corporation, Billerica, USA) overnight at 4°C. The secondary antibody [biotinylated polyvalent antibody, Zytochem Plus (HRP) Broad Spectrum Kit, Zytomed Systems, Berlin, Germany] was incubated for 30 minutes at room temperature, followed by incubation with horseradish peroxidase [Zytochem Plus (HRP) Broad Spectrum Kit] for 15 minutes at room temperature. Antibody binding was visualized using AEC solution (Zytochem Plus HRP Broad Spectrum Kit). Tissues were counterstained with hematoxylin. Immunostaining was confirmed in a series of 'whole tumor sections' to exclude spatial restriction of marker expression in TMAs (not shown). To avoid experimental bias within the set of tumor samples, immunohistochemistry of all examined tissue samples was performed under identical experimental conditions. Immunostaining was assessed by two independent investigators (A.M., T.V.). Cytoplasmic GDF15 and MMP1 staining intensity was estimated using a 5-step scoring system (range 0-4) with regard to staining intensity: 0, negative; 1(+) weakly positive (<50% positive cells and weak intensity); 2 + positive (<50% and moderate); 3 ++ strongly positive (<50% and strong intensity or >50% and weak intensity); 4 +++ very strongly positive (>50% moderate and strong intensity). The Pearson Chi square test was used for statistical analyses, $p<0.05$ was considered significant.

Quantitative real-time RT-PCR

For microarray validation, quantitative real-time RT-PCR (QPCR) was performed as described previously [8]. RNA was isolated from 5 representative MN, 5 PM, and 5 MM that were included before in the microarray analysis. One microgram of RNA was reversely transcribed using the SuperScript II reverse transcription system (Invitrogen, Carlsbad, USA) in combination with random hexa primers. The resulting cDNA was used as template for RT-PCR on an ABI 7000 Sequence Detection System (Applied Biosystem, Foster City, USA). The ddCT method was applied for quantitation of gene expression. Expression signals were normalized to 18S rRNA. The analyses were done in triplicates using commercial TaqMan™ assays (Applied Biosystems) and custom-designed primer pairs (Apara Bioscience,

Denzlingen, Germany): Serpin B3: Hs00199468_m1; Serpin B4: Hs01691258_g1; 18S rRNA: Hs99999901_s1; FRZB proximal forward: 5'-AAACTGTAGAGGGGCAAGCA-3', reverse: 5'-GGCAGCCAGAGCTGGTATAG-3', TLE1 proximal forward: 5'-CACGACTTCACCTCCCAGAT-3', reverse: 5'-CTGGAATATGCTGGCTCCAT-3', CNTN1 proximal forward: 5'-CCCTTTCCCGGTTTACAAAT-3', reverse: 5'-TCAGGTGGGAAAGGATCAAG-3'.

Statistical analysis

Chipinspector version 1.3 (Genomatix Software GmbH, Munich, Germany) was used for single probe based analysis of gained CEL files as described earlier [10]. For testing statistical significance false discovery rate (FDR) was set to 0, minimal probe coverage was set to 3, minimal probe change <-2 and >2. To reveal functional connections between the regulated transcripts, a network and pathway analysis of the pre-filtered genes was performed as described [11] using the Ingenuity™ Pathways Analysis online application (www.ingenuity.com, Ingenuity™ Systems, Mountain View, USA). The significance of networks was calculated by integrated Ingenuity™ algorithms [11]. Principal component analysis (PCA) was performed with Partek Genomic Suite 6.4 (Partek Inc., St. Louis, USA). Comparison of the survival curve with low and high expressing melanoma was performed with SPSS V.18.0 (SPSS Inc., Chicago, USA). Values of $p<0.05$ were considered to be significant. All specimens on the TMAs were considered independently. Progression free survival (PFS) curves comparing patients with GDF15 and MMP1 staining patterns were calculated by the Kaplan–Meier method, with significance evaluated by two-sided log rank statistics as described earlier [12].

Results

Comparative gene expression profiling

To investigate the transcriptional profiles that are associated with malignant progression in melanoma, we compared 18 MN to 20 PM and 20 MM using a single probe based microarray analysis. CEL files were analyzed by Chipinspector version 1.3 (Genomatix Software GmbH, Munich, Germany), which is based on single probe analysis and *de novo* gene annotation that bypasses probe set definitions. After elimination of probes that could cross-hybridize to other transcripts, Chipinspector (CI) identified significantly regulated individual probes using default settings. At least 3 probes had to match per annotated transcript and minimal probe coverage was set to 3 with a fold change of <-2 and >2. In the comparison of PM with MN, Chipinspector identified 52055 probes significantly up- and 48713 probes significantly down-regulated after elimination of probes that could cross-hybridize to other transcripts. We received 691 transcripts matching 284 significantly regulated genes; 167 up- and 117 down-regulated in PM compared to MN. Comparing MM to PM we found 39016 and 35455 probes significantly up- and down-regulated (586 transcripts matching 189 genes, 26 up-, 163 down-regulated in MM compared to PM) (Supplemental Table 1).

Among the 167 genes that were up-regulated in PM compared to MN, we found a high overlap with previously reported genes, e.g. PRAME, SSP1 [13, 14], CXCL9, PHACTR1, CITED-1, BCL2A1 [13, 15] S100A9, MMP1, FN1 [16], NNMT, SERPIN A3 [13], MCAM [17], ISG15 [18], CDK-2, and CDK-4 [19], GDF15 [13, 15, 20] and Hey1 [15, 16]. Comparing genes that were down-regulated from PM to MN with previous studies, we found consensus for CIRBP, FEZ1, PPP1R3C, LDOC1, TRPM1 [16], Desmoglein [17], KRT-15 [13], FABP7 [20], p57KIP2, and CDKN1 [21]. In MM, only a few genes have been described so far to be up-regulated compared to PM. Interestingly, we also found only 26 up-regulated genes. Of these, significant regulation has been described before for VEGFA [22, 23], FN1 [6, 24], IGFBP2 [25], SPP1, MAGEA12, c-MET [6, 15, 26], STC1, and PLOD2 [6]. Down-regulation in MM included the previously published genes Serpin B5 [27], SPRR1A, KRT 16/17/6B, CD 24, LOR, DSC1 [26], KRT 1/14/6A/5, CXCL14 and SPINT2 [6]. For the full list of regulated transcripts, see Supplemental Table 1.

Expression profile-based sample classification

To classify the tumor specimens based on their transcriptional profiles, we used principal component analysis (PCA) anticipating that the specimens would group according to their histological origin, i.e. MN, PM, and MM. Indeed, PCA displayed a clear spatial separation between the three histological entities reflecting considerable differences in respective gene expression signatures. The most significant difference was seen between PM and MN (Supplemental Figure 1) confirming previous data of our group [7] which pointed out that gene expression patterns differ dramatically between MN and PM and not so much between PM and MM.

Identification of signaling pathways and networks

To further unravel functions and networks of the regulated transcripts, we mapped the microarray 'hits' according to biological functions in Ingenuity's™ Knowledge Base. Comparing PM to MN, particularly such genes were differentially regulated that play a role in cancer, dermatological diseases and conditions, cellular growth and proliferation, cellular movement, inflammatory response (Supplemental Table 2). Applying Ingenuity's Network Algorithm™, 15 functional gene networks could be constituted in total. Each of them contained more than 10 regulated focus genes with significant Ingenuity scores [11] of 11 and more (for example, maximum score of network 1 was 42, see Supplemental Figure 2A). Within these networks several genes were comprised with known relevance for melanoma biology, e.g. SPP1, STAT1, MMP1, or CDK2. Consequently, we found an affection of canonical pathways that are known to play a role in melanoma development, such as MAPK-signaling, apoptosis, Notch-, WNT/beta catenin- and integrin-signaling, as well as G1/S and G2/M checkpoint control [28, 29] (Table 2). When we grouped the 189 genes that were differentially regulated between MM and PM according to biological functions in Ingenuity's™ Knowledge Base, we found an association to hair and skin development and function, dermatological diseases and conditions, cancer, cellular development, cellular movement, cellular growth and proliferation and inflammatory response (Supplemental Table 3). Also in MM, these functions were linked to melanoma-typical signaling pathways such as WNT/beta catenin-, integrin-, VEGF-, PI3/AKT- and cell-to-cell signaling (Table 2, Supplemental Figure 2B).

Novel melanoma-associated genes

To filter out novel genes with relevance for melanoma, we performed a separate Ingenuity™ pathway analysis that only comprised the most significant transcripts, i.e. showing an up- and down-regulation with a minimum log ratio of 1.5 (Supplemental Figure 2C). Based on our comprehensive GO analysis (Table 2), we primarily expected to find genes with relationship to major melanoma pathways like MAPK-, Notch- or Wnt-signaling. Indeed, we found a relatively new player of the Notch pathway, the cell adhesion molecule contactin 1 (CNTN1), to be significantly down-regulated in PM compared to MN. In the Wnt/beta catenin pathway, we found frizzled-related protein (FRZB) and the tranducin-like enhancer of split 1 (TLE1) to be differentially expressed (both down in PM). Also included in the strongest up-regulated genes in PM, we found the Serpin peptidase inhibitors Serpin B3 and B4, both–linked to MAPK signaling [30]. At last, we could confirm the recently described up-regulation of the TGF-β family member growth differentiation factor 15 (GDF15) in PM [13, 15, 16].

To verify the expression levels of FRZB, TLE1, CNTN1, Serpin B3 and Serpin B4 we performed quantitative real-time RT-PCR (QPCR) using the same mRNA templates as for the microarrays. The down-regulation of FRZB, TLE1, and CNTN1 from benign MN to malignant PM and MM was largely confirmed with high statistical significance (Supplemental Figure 3). Also in case of Serpin B4, the up-regulation in PM compared to MN and MM could be reproduced by QPCR ($p=0.028$ and $p=0.001$, respectively). The Serpin B3-QPCR confirmed the significant down-regulation in MM compared to PM ($p=0.001$) and showed a trend towards up-regulation in PM ($p=0.422$).

For proof-of-principle that the observed transcriptional changes also translate into different protein levels, we picked one candidate marker with particularly interesting biology, GDF15 (up-regulated in melanoma), for further tissue microarray analysis (Figure 1). As control gene with known regulation, MMP1 was selected. Two independent investigators (A.M., T.V.) evaluated immunostaining of >280 human tissue specimens based on a 5-step scoring system (for details, see *Methods*, Supplemental Table 4). Inter- and intra-examiner reproducibility was 86.2 % (GDF15) and 79.5 % (MMP1), respectively. In accordance with the microarray data, PM and MM revealed a high expression of GDF15 protein (average scores 2.52 and 2.21, respectively), whereas GDF15 expression in MN was almost negligible (average score 0.91). The differences in expression were highly significant with $p=1.8$ E-20 for MN vs. PM and $p<0.05$ for PM vs. MM, respectively (Chi square test). To our knowledge this is the first

time that GDF15 protein expression was analyzed in a large panel of melanocytic tumors. Interestingly, progression free survival (PFS) in melanoma patients with low GDF15 staining (0 to 2+) was significantly higher compared to patients with high GDF15 expression (3+ to 4+) (p=0.037; Figure 2A). Confirming previous reports on matrix metalloproteinases [31, 32], we observed a high immunoreactivity for MMP1 in PM (average score 3.02) with a significant decrease in MM (2.46, p=1.26 E-5, Chi square test) and MN (mean 2.29, p=2 E-12, Chi square test). Here, no significant difference in PFS was observed between melanoma patients with low and high MMP1 (Figure 2B).

Discussion

In this study, we performed gene expression profiling and computational network analysis of a large series of patient samples derived from MN, PM and MM to gain new insights into melanoma biology. Our experiments discovered a panel of new candidate markers that are associated with melanoma-relevant signaling pathways such as MAPK-, Notch-, and Wnt-signaling.

Since the discovery of activating BRAF mutations in high percentage of melanoma [33-35], the MAPK signal transduction (with its various cascades of MAPKKKs, MAPKKs, and MAPKs) has been put into focus of melanoma research, not least, because of its highly drug-targetable potential. However, recent failures in BRAF-targeting therapy [4] disclosed our considerable lack in understanding this pathway and its interaction with other signaling networks [5]. As expected, also in our set of samples, we found differential expression of genes with known association to MAPK signaling. For example, STAT1 and SPP1 were up-regulated in PM compared to MN whereas PPP1R3C was down-regulated. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus, where they act as transcription activators. In former studies, SPP1 was found to be strongly up-regulated in PM and MM [6, 13, 36], which is in accordance with our data. Little is known about the function and role of PPP1R3C in human cancer. It is supposed to have tumor suppressor function since promoter hypermethylation and reduced mRNA expression were shown in melanoma compared to melanocytes [37].

As novel progression-related markers with association to MAPK signaling, we identified two Serpin peptidase inhibitors, Serpin B3 (squamous cell carcinoma antigen 1, SCCA1) and Serpin B4 (SCCA2, leupin). Both were strongly up-regulated in PM compared to MN and down-regulated in MM. Recently, it has been shown that Serpin B3 is a specific endogenous inhibitor of c-Jun-NH²-terminal kinase-1 (JNK1/MAPK8) and protects UV-exposed keratinocytes from apoptotic cell death after sun exposure [38]. Little is known about the role of Serpin B3 and Serpin B4 in melanoma. In squamous cell carcinomas of the cervix, lung, head and neck, however, Serpin B3 is already used as a tumor marker [39, 40]. Serpin B4 could be a general marker for tumor invasion and metastasis because its suppression by antisense cDNA, e.g. in uterine cancer cells, is followed by a decrease of E-cadherin

expression, which determines a common step in loss of cell-cell adhesion [41]. Since also melanoma cells can escape from keratinocyte control through down-regulation of E-cadherin [17], we assume that Serpins play an important role also during melanoma progression. This conclusion is further supported by our observation that another family member, Serpin B5 (maspin), was additionally decreased in MMs. Loss of Serpin B5 is another marker for invasion and migration in a variety of other tumors such as breast, prostate, and pancreatic cancer [42].

Next to the MAPK pathway, TGF-β signaling is critical for tumor cell invasion and metastasis [43]. We found GDF15, a member of the TGF-β superfamily, to be dramatically up-regulated in PM and MM compared to MN. In addition, we found that low GDF15 expression in melanoma patients is associated with higher progression free survival compared to high GDF15 expression. This matches previous reports on GDF15 suggesting a role in invasiveness of gastric cancer cells through up-regulation of the urokinase-type plasminogen activator system in an ERK1/2- dependent pathway [44]. Just recently, Boyle and co-workers started to mechanistically unravel the role of GDF15 in melanoma. They showed that shRNA knockdown in three different melanoma cell lines resulted in significantly decreased tumorigenicity in a mouse xenograft model [45]. This is also in accordance with a former finding by Talantov et al. who proposed that GDF15 is a better marker for differentiation between melanomas from benign nevi than the conventional markers tyrosinase, me20m and MART1 [15]. Because of its additional connection to other cancer pathways such as p53 [46], MITF [47], and PI3K/AKT signaling [45, 48, 49], it may represent a new key player in the development of metastatic melanoma associated with poor prognosis and survival [50].

With FRZB and TLE1 we also detected two players of the Wnt signaling pathway to be down-regulated in PM compared to MN. FRZB (sFRP3) belongs to the secreted Frizzled-related protein family, whose members prevent ligand-receptor interaction by binding to extracellular Wnt ligands [51, 52]. It has been suggested that FRZB exhibits tumor suppressor activity since down-regulation of FRZB has been shown to be involved in pleural mesothelioma [53] and prostate cancer [54]. TLE1 is a member of the Groucho/TLE/Grg family of corepressors that operate in many signaling pathways [55, 56]. It has important transcription factor partners, e.g. TCF/LEF-1 in the case of the Wnt signaling pathway [57]. TLE1 inactivation was suggested to contribute to the development of hematologic

malignancies by disrupting critical differentiation and growth suppressing pathways [58]. In Notch signaling, TLE1 functions as a co-repressor for HES1, which is activated in some human malignancies and allows tumor cells to evade differentiation and irreversible cell cycle arrest [52, 59]. Although there is increasing evidence for the critical role of Wnt signaling in tumor development, there are only a few studies available on Wnt in melanoma [60-63]. According to our data, particularly FRZB and TLE1 would represent promising future study targets in this context.

CNTN1, a member of the immunoglobulin superfamily, is a GPI- anchored neuronal membrane protein that functions as a cell adhesion molecule and acts as a functional ligand for Notch, e.g. during oligodendrocyte maturation [64]. Depending on the tissue context, Notch signaling can exhibit tumor initiating or tumor suppressive properties through complex modulation of tumor cell differentiation, proliferation, and apoptosis [65, 66]. In melanoma, activation of Notch signaling seems to be important throughout tumor progression. For example, stable overexpression of Nic, the active form of Notch, in benign melanocytes leads to transformation into a malignant phenotype whereas activation of Notch1 in primary melanoma cells resulted in a more metastatic phenotype [67, 68]. Hence, CNTN1 could be a so far overlooked critical progression factor in melanoma and should be investigated in follow up studies.

In confirmation with previous profiling studies by others and us, the present data support the concept that primary and metastatic melanomas are characterized by distinct gene expression patterns, in particular when compared to benign melanocytic nevi. These expression patterns reflect the activation/deactivation of cancer signaling pathways that are well-known for melanoma, such as MAPK-, Wnt-, or Notch-signaling. However, novel molecular players are still emerging and need to be further evaluated to get a better and more comprehensive understanding of melanoma for future diagnostics and therapy.

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Characteristics		PM (%)	MM (%)	MN (%)
Tissue samples		20	20	18
Mean age		68.5 +-13.4	55 +- 15.63	23.33 +- 13.6
Gender				
	Female	10 (50)	4 (29)	8 (50)
	Male	10 (50)	10 (71)	8 (50)
PM subtypes				
	ALM	2 (10)		
	LMM	3 (15)		
	NMM	4 (20)		
	SNM	5 (25)		
	SSM	6 (30)		
Tumor thickness according to Breslow				
	≤1mm	4 (20)		
	1-2mm	4 (20)		
	≥2mm	12 (60)		
Clark Level				
	I			
	II			
	III	3 (15)		
	IV	13 (65)		
	V	4 (20)		
T stage				
	T1	4 (20)		
	T2	6 (30)		
	T3	4 (20)		
	T4	6 (30)		

Table 1: Patient information with PM subtypes (ALM= acral lentiginous melanoma; LMM= lentigo maligna melanoma; NMM= nodular melanoma; SNM= secondary nodular melanoma; SSM= superficial spreading melanoma).

Pathway	PM c/t MN	MM c/t PM
MAPK	(e.g. STAT1 ↑, SPP1 ↑, PPP1R3C ↓, GDF15 ↑, MMP1 ↑, Serpin B3 ↑ , Serpin B4 ↑)	(Serpin B3 ↓, Serpin B4 ↓)
PI3/AKT		(e.g. SFN ↓)
Cell cycle control	(e.g. cyclin B1 ↑, cyclin B2 ↑, CDKN1C↓, CDK2 ↑)	(e.g. SFN ↓)
Apoptosis	(e.g. SPP1 ↑, TNFRSF21 ↑, BCL2A1 ↑)	
Cell-cell adhesion		(e.g. E-cadherin ↓, P-cadherin ↓)
Wnt	(e.g. TLE1 ↓, FRZB ↓)	(e.g. E-cadherin ↓, P-cadherin ↓)
Notch	(e.g. CNTN1↓, HEY1 ↑)	
Integrin	(e.g. ACTN1 ↑,ITGB2↑, FN1 ↑, LAMB4 ↓, COL4A1 ↑, COL4A2 ↑)	(e.g. FN1 ↑, LAMC2 ↓, LAMA3 ↓)
VEGF		(e.g. VEGFA ↑)

Table 2: Melanoma-typic pathways are found regulated within the set of differentially expressed genes. ↑↓ refers to up- or down-regulated genes in PM (column 2), MM (column 3)

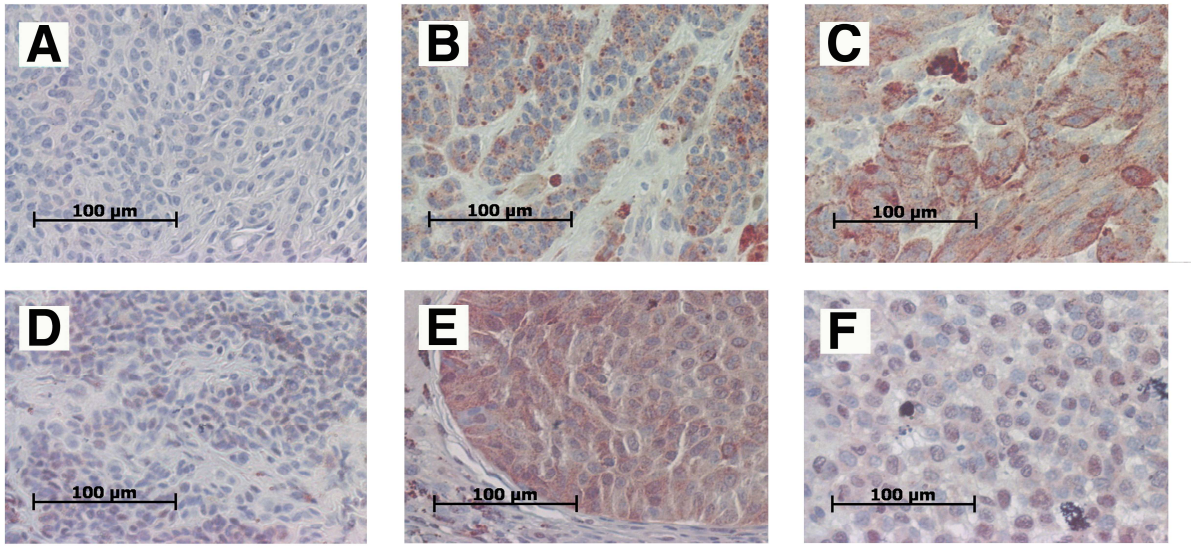


Figure 1: Immunohistochemical staining of GDF15 (A, B, C) and MMP1 (D, E, F) based on a 5-step scoring system (range 0-4+). Negative staining of GDF15 in a MN (A), positive (4+) staining in a PM (B) and MM (C), positive (2+) staining of MMP1 in a MN (D), positive (4+) staining in a PM (E) and positive (2+) staining in a MM (F). Original magnification x 200.

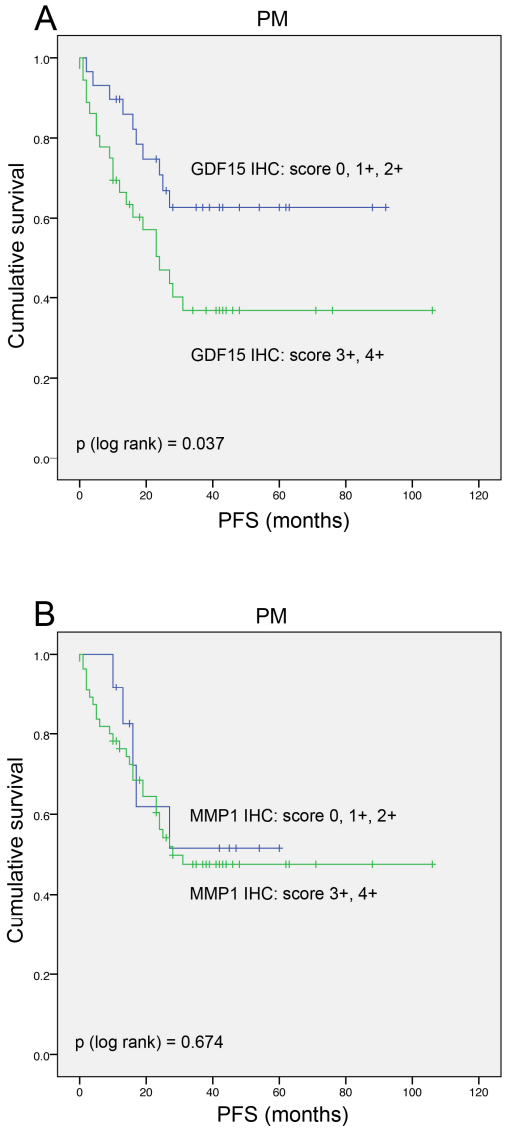


Figure 2: Distribution of time (months) to melanoma progression among patients with low (0, 1+, 2+) and high (3+, 4+) immunoreactivity as estimated by the Kaplan-Meier method. IHC, immunohistochemistry; PFS, progression free survival. (A) GDF15 staining; (B) MMP1 staining.

Search Term	Gene Id	Symbol	Gene Name	logRatio PM minus MN	Fold change
Gene up regulated in PM compared to MN					
23532	23532	PRAME	preferentially expressed antigen in melanoma	3.297	9.82869584
6696	6696	SPP1	secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	2.815	7.03719261
4283	4283	CXCL9	chemokine (C-X-C motif) ligand 9	2.743	6.69460994
221692	221692	PHACTR1	phosphatase and actin regulator 1	2.628	6.1816844
6280	6280	S100A9	S100 calcium binding protein A9	2.628	6.1816844
4312	4312	MMP1	matrix metallopeptidase 1 (interstitial collagenase)	2.624	6.16456887
3854	3854	KRT6B	keratin 6B	2.474	5.55582054
10537	10537	UBD	ubiquitin D	2.349	5.0947099
7453	7453	WARS	tryptophanyl-tRNA synthetase	2.263	4.79988553
6318	6318	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	2.256	4.77665275
3627	3627	CXCL10	chemokine (C-X-C motif) ligand 10	2.121	4.34995356
5996	5996	RGS1	regulator of G-protein signalling 1	2.106	4.3049605
2335	2335	FN1	fibronectin 1	2.102	4.29304115
3868	3868	KRT16	keratin 16 (focal non-epidermolytic palmoplantar keratoderma)	2.091	4.26043281
3853	3853	KRT6A	keratin 6A	2.087	4.24863675
6698	6698	SPRR1A	small proline-rich protein 1A	2.061	4.17275437
9518	9518	GDF15	growth differentiation factor 15	2.037	4.10391258
2	2	A2M	alpha-2-macroglobulin	1.987	3.96411825
713	713	C1QB	complement component 1, q subcomponent, B chain	1.936	3.82643263
5266	5266	PI3	peptidase inhibitor 3, skin-derived (SKALP)	1.841	3.58258268
91316	91316	LOC91316	similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)	1.829	3.55290718
3371	3371	TNC	tenascin C (hexabrachion)	1.79	3.45814893
3492	3492	IGH@	immunoglobulin heavy locus	1.785	3.44618464
27299	27299	ADAMDEC1	ADAM-like, decysin 1	1.78	3.43426175
6279	6279	S100A8	S100 calcium binding protein A8	1.724	3.30351066
91353	91353	CTA-246H3.1	similar to omega protein	1.685	3.21540396
10563	10563	CXCL13	chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)	1.66	3.16016525
712	712	C1QA	complement component 1, q subcomponent, A chain	1.63	3.09512999
9232	9232	PTTG1	pituitary tumor-transforming 1	1.615	3.06311599
6241	6241	RRM2	ribonucleotide reductase M2 polypeptide	1.593	3.01676015
3937	3937	LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	1.557	2.94241349
6699	6699	SPRR1B	small proline-rich protein 1B (cornifin)	1.55	2.92817139
6317	6317	SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	1.54	2.90794503
4837	4837	NNMT	nicotinamide N-methyltransferase	1.52	2.8679105
55872	55872	PBK	PDZ binding kinase	1.506	2.84021472
3838	3838	KPNA2	karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	1.487	2.8030549
4435	4435	CITED1	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1	1.481	2.79142153
7037	7037	TFRC	transferrin receptor (p90, CD71)	1.475	2.77983644
3872	3872	KRT17	keratin 17	1.474	2.77791027
3429	3429	IFI27	interferon, alpha-inducible protein 27	1.469	2.76829943
597	597	BCL2A1	BCL2-related protein A1	1.466	2.7625489
10437	10437	IFI30	interferon, gamma-inducible protein 30	1.462	2.75490009
6772	6772	STAT1	signal transducer and activator of transcription 1, 91kDa	1.46	2.75108364
3512	3512	IGJ	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	1.456	2.74346658
11065	11065	UBE2C	ubiquitin-conjugating enzyme E2C	1.449	2.73018744
3595	3595	IL12RB2	interleukin 12 receptor, beta 2	1.448	2.72829567
7378	7378	UPP1	uridine phosphorylase 1	1.448	2.72829567
7262	7262	PHLDA2	pleckstrin homology-like domain, family A, member 2	1.436	2.70569646
963	963	CD53	CD53 molecule	1.422	2.6795672
23327	23327	NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like	1.402	2.64267681
2633	2633	GBP1	guanylate binding protein 1, interferon-inducible, 67kDa	1.383	2.60810147
2537	2537	IFI6	interferon, alpha-inducible protein 6	1.382	2.6062943
7805	7805	LAPTM5	lysosomal associated multispanning membrane protein 5	1.378	2.59907812
1508	1508	CTSB	cathepsin B	1.377	2.59727721
6362	6362	CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	1.369	2.5829147
813	813	CALU	calumenin	1.369	2.5829147

4162	4162	MCAM	melanoma cell adhesion molecule	1.362	2.57041267
3108	3108	HLA-DMA	major histocompatibility complex, class II, DM alpha	1.356	2.55974483
9636	9636	ISG15	ISG15 ubiquitin-like modifier	1.355	2.55797116
2207	2207	FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	1.351	2.55088878
822	822	CAPG	capping protein (actin filament), gelsolin-like	1.344	2.53854177
6947	6947	TCN1	transcobalamin I (vitamin B12 binding protein, R binder family)	1.343	2.5367828
929	929	CD14	CD14 molecule	1.343	2.5367828
1687	1687	DFNA5	deafness, autosomal dominant 5	1.339	2.52975908
6363	6363	CCL19	chemokine (C-C motif) ligand 19	1.331	2.51576994
1282	1282	COL4A1	collagen, type IV, alpha 1	1.32	2.4966611
891	891	CCNB1	cyclin B1	1.314	2.48629934
9332	9332	CD163	CD163 molecule	1.293	2.45037066
1164	1164	CKS2	CDC28 protein kinase regulatory subunit 2	1.291	2.44697608
11015	11015	KDELR3	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	1.288	2.44189303
6574	6574	SLC20A1	solute carrier family 20 (phosphate transporter), member 1	1.287	2.44020102
22996	22996	C1orf34	chromosome 1 open reading frame 34	1.284	2.43513204
5653	5653	KLK6	kallikrein-related peptidase 6	1.282	2.43175857
6035	6035	RNASE1	ribonuclease, RNase A family, 1 (pancreatic)	1.279	2.42670712
684	684	BST2	bone marrow stromal cell antigen 2	1.273	2.41663569
6352	6352	CCL5	chemokine (C-C motif) ligand 5	1.271	2.41328784
914	914	CD2	CD2 molecule	1.26	2.39495741
22974	22974	TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	1.259	2.39329793
6955	6955	TRA@	T cell receptor alpha locus	1.258	2.39163959
51303	51303	FKBP11	FK506 binding protein 11, 19 kDa	1.254	2.38501774
55379	55379	LRRC59	leucine rich repeat containing 59	1.249	2.37676621
962	962	CD48	CD48 molecule	1.239	2.36034869
3778	3778	KCNMA1	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	1.234	2.3521825
9133	9133	CCNB2	cyclin B2	1.232	2.34892394
55062	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	1.229	2.34404457
5698	5698	PSMB9	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	1.226	2.33917533
5315	5315	PKM2	pyruvate kinase, muscle	1.225	2.3375545
51514	51514	DTL	denticleless homolog (Drosophila)	1.224	2.33593479
57103	57103	C12orf5	chromosome 12 open reading frame 5	1.211	2.31498043
7298	7298	TYMS	thymidylate synthetase	1.209	2.31177341
344	344	APOC2	apolipoprotein C-II	1.204	2.30377528
9404	9404	LPXN	leupaxin	1.204	2.30377528
7305	7305	TYROBP	TYRO protein tyrosine kinase binding protein	1.204	2.30377528
3576	3576	IL8	interleukin 8	1.198	2.29421405
9768	9768	KIAA0101	KIAA0101	1.198	2.29421405
23406	23406	COTL1	coactosin-like 1 (Dictyostelium)	1.197	2.29262437
3001	3001	GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	1.197	2.29262437
9787	9787	DLG7	discs, large homolog 7 (Drosophila)	1.193	2.28627667
5327	5327	PLAT	plasminogen activator, tissue	1.183	2.2704842
4318	4318	MMP9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	1.174	2.25636427
3059	3059	HCLS1	hematopoietic cell-specific Lyn substrate 1	1.172	2.25323846
397	397	ARHGDIB	Rho GDP dissociation inhibitor (GDI) beta	1.159	2.23302592
972	972	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	1.157	2.22993244
9833	9833	MELK	maternal embryonic leucine zipper kinase	1.157	2.22993244
1284	1284	COL4A2	collagen, type IV, alpha 2	1.156	2.2283873
6790	6790	AURKA	aurora kinase A	1.152	2.22221746
4069	4069	LYZ	lysozyme (renal amyloidosis)	1.15	2.21913894
87	87	ACTN1	actinin, alpha 1	1.146	2.21299471
23462	23462	HEY1	hairy/enhancer-of-split related with YRPW motif 1	1.143	2.20839769
1017	1017	CDK2	cyclin-dependent kinase 2	1.141	2.20533833
1033	1033	CDKN3	cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)	1.141	2.20533833
4939	4939	OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	1.134	2.19466388
6890	6890	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	1.133	2.19314318
3669	3669	ISG20	interferon stimulated exonuclease gene 20kDa	1.13	2.1885874
27242	27242	TNFRSF21	tumor necrosis factor receptor superfamily, member 21	1.128	2.18555548

4111	4111	MAGEA12	melanoma antigen family A, 12	1.127	2.18404109
6490	6490	SILV	silver homolog (mouse)	1.121	2.17497678
11332	11332	ACOT7	acyl-CoA thioesterase 7	1.121	2.17497678
3003	3003	GZMK	granzyme K (granzyme 3; tryptase II)	1.121	2.17497678
51338	51338	MS4A4A	membrane-spanning 4-domains, subfamily A, member 4	1.119	2.17196371
6271	6271	S100A1	S100 calcium binding protein A1	1.119	2.17196371
6347	6347	CCL2	chemokine (C-C motif) ligand 2	1.114	2.16444929
3959	3959	LGALS3BP	lectin, galactoside-binding, soluble, 3 binding protein	1.114	2.16444929
57016	57016	AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	1.104	2.14949835
12	12	SERPINA3	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	1.099	2.14206165
3002	3002	GZMB	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)	1.087	2.12431837
7852	7852	CXCR4	chemokine (C-X-C motif) receptor 4	1.084	2.11990557
3394	3394	IRF8	interferon regulatory factor 8	1.08	2.11403608
6373	6373	CXCL11	chemokine (C-X-C motif) ligand 11	1.075	2.10672207
10095	10095	ARPC1B	actin related protein 2/3 complex, subunit 1B, 41kDa	1.071	2.10088909
5265	5265	SERPINA1	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	1.071	2.10088909
5214	5214	PFKP	phosphofructokinase, platelet	1.069	2.09797866
3123	3123	HLA-DRB1	major histocompatibility complex, class II, DR beta 1	1.067	2.09507225
51056	51056	LAP3	leucine aminopeptidase 3	1.065	2.09216988
6402	6402	SELL	selectin L (lymphocyte adhesion molecule 1)	1.064	2.0907202
533	533	ATP6V0B	ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b	1.064	2.0907202
58986	58986	TMEM8	transmembrane protein 8 (five membrane-spanning domains)	1.062	2.08782385
717	717	C2	complement component 2	1.061	2.08637719
8836	8836	GGH	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	1.057	2.08060053
11031	11031	RAB31	RAB31, member RAS oncogene family	1.056	2.07915887
51330	51330	TNFRSF12A	tumor necrosis factor receptor superfamily, member 12A	1.056	2.07915887
9263	9263	STK17A	serine/threonine kinase 17a	1.055	2.07771821
3122	3122	HLA-DRA	major histocompatibility complex, class II, DR alpha	1.044	2.06193664
948	948	CD36	CD36 molecule (thrombospondin receptor)	1.041	2.05765342
1893	1893	ECM1	extracellular matrix protein 1	1.04	2.05622765
3689	3689	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	1.04	2.05622765
11145	11145	HRASLS3	HRAS-like suppressor 3	1.034	2.0476938
10962	10962	MLLT11	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11	1.033	2.04627494
4314	4314	MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	1.032	2.04485706
915	915	CD3D	CD3d molecule, delta (CD3-TCR complex)	1.031	2.04344017
3113	3113	HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	1.026	2.0363704
6999	6999	TDO2	tryptophan 2,3-dioxygenase	1.025	2.03495938
3109	3109	HLA-DMB	major histocompatibility complex, class II, DM beta	1.019	2.0265138
1123	1123	CHN1	chimerin (chimaerin) 1	1.019	2.0265138
8870	8870	IER3	immediate early response 3	1.018	2.02510961
2745	2745	GLRX	glutaredoxin (thioltransferase)	1.018	2.02510961
79139	79139	DERL1	Der1-like domain family, member 1	1.01	2.0139111
3713	3713	IVL	involucrin	1.01	2.0139111
332	332	BIRC5	baculoviral IAP repeat-containing 5 (survivin)	1.009	2.01251565
1503	1503	CTPS	CTP synthase	1.007	2.00972764
1601	1601	DAB2	disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	1.006	2.00833509
9055	9055	PRC1	protein regulator of cytokinesis 1	1.006	2.00833509
10112	10112	KIF20A	kinesin family member 20A	1.006	2.00833509
1476	1476	CSTB	cystatin B (stefin B)	1.005	2.0069435
29887	29887	SNX10	sorting nexin 10	1.003	2.00416321
5641	5641	LGMN	legumain	1.001	2.00138677
5476	5476	CTSA	cathepsin A	1	2
Gene down regulated in PM compared to MN					
6137	6137	RPL13	ribosomal protein L13	-1.004	2.00555287
80201	80201	HKDC1	hexokinase domain containing 1	-1.005	2.0069435
4501	4501	MT1X	metallothionein 1X	-1.005	2.0069435
29997	29997	GLTSCR2	glioma tumor suppressor candidate region gene 2	-1.005	2.0069435
5803	5803	PTPRZ1	protein tyrosine phosphatase, receptor-type, Z polypeptide 1	-1.013	2.01810327
91851	91851	CHRDL1	chordin-like 1	-1.014	2.0195026

23650	23650	TRIM29	tripartite motif-containing 29	-1.016	2.02230416
10351	10351	ABCA8	ATP-binding cassette, sub-family A (ABC1), member 8	-1.019	2.0265138
2628	2628	GATM	glycine amidinotransferase (L-arginine:glycine amidinotransferase)	-1.021	2.02932509
3590	3590	IL11RA	interleukin 11 receptor, alpha	-1.024	2.03354935
6304	6304	SATB1	SATB homeobox 1	-1.029	2.04060932
23461	23461	ABCA5	ATP-binding cassette, sub-family A (ABC1), member 5	-1.031	2.04344017
120	120	ADD3	adducin 3 (gamma)	-1.033	2.04627494
3480	3480	IGF1R	insulin-like growth factor 1 receptor	-1.033	2.04627494
55638	55638	FLJ20366	hypothetical protein FLJ20366	-1.034	2.0476938
92211	92211	PCDH21	protocadherin 21	-1.037	2.05195629
23705	23705	CADM1	cell adhesion molecule 1	-1.037	2.05195629
1153	1153	CIRBP	cold inducible RNA binding protein	-1.039	2.05480288
9638	9638	FEZ1	fasciculation and elongation protein zeta 1 (zygin I)	-1.04	2.05622765
3316	3316	HSPB2	heat shock 27kDa protein 2	-1.044	2.06193664
7102	7102	TSPAN7	tetraspanin 7	-1.045	2.06336636
10278	10278	EFS	embryonal Fyn-associated substrate	-1.047	2.06622878
5325	5325	PLAGL1	pleiomorphic adenoma gene-like 1	-1.048	2.06766147
2947	2947	GSTM3	glutathione S-transferase M3 (brain)	-1.049	2.06909516
7306	7306	TYRP1	tyrosinase-related protein 1	-1.049	2.06909516
55366	55366	LGR4	leucine-rich repeat-containing G protein-coupled receptor 4	-1.054	2.07627854
56967	56967	C14orf132	chromosome 14 open reading frame 132	-1.057	2.08060053
81578	81578	COL21A1	collagen, type XXI, alpha 1	-1.057	2.08060053
23075	23075	SWAP70	SWAP-70 protein	-1.069	2.09797866
3131	3131	HLF	hepatic leukemia factor	-1.071	2.10088909
51309	51309	ARMCX1	armadillo repeat containing, X-linked 1	-1.074	2.10526231
23037	23037	PDZD2	PDZ domain containing 2	-1.076	2.10818285
1474	1474	CST6	cystatin E/M	-1.083	2.11843667
23641	23641	LDOC1	leucine zipper, down-regulated in cancer 1	-1.088	2.12579135
224	224	ALDH3A2	aldehyde dehydrogenase 3 family, member A2	-1.092	2.13169347
1028	1028	CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	-1.098	2.1405774
84909	84909	C9orf3	chromosome 9 open reading frame 3	-1.11	2.15845647
1828	1828	DSG1	desmoglein 1	-1.113	2.16294953
7991	7991	TUSC3	tumor suppressor candidate 3	-1.115	2.16595009
79652	79652	C16orf30	chromosome 16 open reading frame 30	-1.124	2.17950422
7704	7704	ZBTB16	zinc finger and BTB domain containing 16	-1.126	2.18252775
26053	26053	AUTS2	autism susceptibility candidate 2	-1.129	2.18707091
7101	7101	NR2E1	nuclear receptor subfamily 2, group E, member 1	-1.129	2.18707091
22798	22798	LAMB4	laminin, beta 4	-1.134	2.19466388
23678	23678	SGK3	serum/glucocorticoid regulated kinase family, member 3	-1.136	2.19770844
1832	1832	DSP	desmoplakin	-1.138	2.20075722
25854	25854	DKFZP564J102	DKFZP564J102 protein	-1.14	2.20381023
1974	1974	EIF4A2	eukaryotic translation initiation factor 4A, isoform 2	-1.145	2.21146131
8796	8796	SCEL	sciellin	-1.156	2.2283873
6662	6662	SOX9	SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)	-1.156	2.2283873
7088	7088	TLE1	transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	-1.163	2.23922578
738	738	C11orf2	chromosome 11 open reading frame2	-1.168	2.24699981
2153	2153	F5	coagulation factor V (proaccelerin, labile factor)	-1.169	2.24855785
51302	51302	CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	-1.177	2.26106113
9890	9890	LPPR4	plasticity related gene 1	-1.186	2.27521046
563	563	AZGP1	alpha-2-glycoprotein 1, zinc-binding	-1.187	2.27678806
114088	114088	TRIM9	tripartite motif-containing 9	-1.194	2.28786195
4897	4897	NRCAM	neuronal cell adhesion molecule	-1.195	2.28944832
9413	9413	C9orf61	chromosome 9 open reading frame 61	-1.197	2.29262437
23635	23635	SSBP2	single-stranded DNA binding protein 2	-1.207	2.30857084
65982	65982	ZSCAN18	zinc finger and SCAN domain containing 18	-1.218	2.32624008
1823	1823	DSC1	desmocollin 1	-1.245	2.37018554
3400	3400	ID4	inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	-1.269	2.40994463
2261	2261	FGFR3	fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	-1.269	2.40994463
55227	55227	LRRC1	leucine rich repeat containing 1	-1.271	2.41328784
1825	1825	DSC3	desmocollin 3	-1.274	2.41831135
3861	3861	KRT14	keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner)	-1.275	2.41998818
25875	25875	LETMD1	LETM1 domain containing 1	-1.282	2.43175857

1308	1308	COL17A1	collagen, type XVII, alpha 1	-1.292	2.44867278
8470	8470	SORBS2	sorbin and SH3 domain containing 2	-1.299	2.46058269
4014	4014	LOR	loricrin	-1.3	2.46228883
80310	80310	PDGFD	platelet derived growth factor D	-1.303	2.46741434
259217	259217	HSPA12A	heat shock 70kDa protein 12A	-1.306	2.47255052
51765	51765	RP6-213H19.1	serine/threonine protein kinase MST4	-1.32	2.4966611
23382	23382	KIAA0828	adenosylhomocysteinase 3	-1.329	2.51228476
4023	4023	LPL	lipoprotein lipase	-1.33	2.51402675
2878	2878	GPX3	glutathione peroxidase 3 (plasma)	-1.345	2.54030197
3769	3769	KCNJ13	potassium inwardly-rectifying channel, subfamily J, member 13	-1.347	2.54382601
3852	3852	KRT5	keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types)	-1.349	2.54735495
51673	51673	CGI-38	brain specific protein	-1.355	2.55797116
5836	5836	PYGL	phosphorylase, glycogen; liver (Hers disease, glycogen storage disease type VI)	-1.366	2.57754926
2625	2625	GATA3	GATA binding protein 3	-1.377	2.59727721
113146	113146	C14orf78	chromosome 14 open reading frame 78	-1.401	2.64084568
8404	8404	SPARCL1	SPARC-like 1 (mast9, hevin)	-1.403	2.64450921
5348	5348	FXYD1	FXYD domain containing ion transport regulator 1 (phospholemman)	-1.41	2.65737163
3080	3080	CFHR2	complement factor H-related 2	-1.435	2.70382167
63928	63928	LOC63928	hepatocellular carcinoma antigen gene 520	-1.45	2.73208051
688	688	KLF5	Kruppel-like factor 5 (intestinal)	-1.456	2.74346658
10218	10218	ANGPTL7	angiopoietin-like 7	-1.46	2.75108364
9355	9355	LHX2	LIM homeobox 2	-1.499	2.82646729
667	667	DST	dystonin	-1.506	2.84021472
83604	83604	TMEM47	transmembrane protein 47	-1.533	2.89386977
1272	1272	CNTN1	contactin 1	-1.542	2.9119791
1428	1428	CRYM	crystallin, mu	-1.561	2.95058291
3849	3849	KRT2	keratin 2 (epidermal ichthyosis bullosa of Siemens)	-1.574	2.97729051
23086	23086	EXPH5	exophilin 5	-1.608	3.04828966
9547	9547	CXCL14	chemokine (C-X-C motif) ligand 14	-1.619	3.07162054
2487	2487	FRZB	frizzled-related protein	-1.642	3.12098192
4308	4308	TRPM1	transient receptor potential cation channel, subfamily M, member 1	-1.646	3.12964713
5507	5507	PPP1R3C	protein phosphatase 1, regulatory (inhibitor) subunit 3C	-1.66	3.16016525
10391	10391	CORO2B	coronin, actin binding protein, 2B	-1.664	3.16893924
2259	2259	FGF14	fibroblast growth factor 14	-1.673	3.18876991
445	445	ASS1	argininosuccinate synthetase 1	-1.697	3.24226048
4118	4118	MAL	mal, T-cell differentiation protein	-1.711	3.27387673
10850	10850	CCL27	chemokine (C-C motif) ligand 27	-1.756	3.37760355
3848	3848	KRT1	keratin 1 (epidermolytic hyperkeratosis)	-1.77	3.41053957
55118	55118	CRTAC1	cartilage acidic protein 1	-1.776	3.42475314
11341	11341	SCRG1	scrapie responsive protein 1	-1.956	3.87984764
2861	2861	GPR37	G protein-coupled receptor 37 (endothelin receptor type B-like)	-1.957	3.88253788
25891	25891	DKFZP586H2123	regeneration associated muscle protease	-1.976	3.9340083
64131	64131	XYLT1	xylosyltransferase I	-1.985	3.95862663
2173	2173	FABP7	fatty acid binding protein 7, brain	-2.009	4.02503129
10752	10752	CHL1	cell adhesion molecule with homology to L1CAM (close homolog of L1)	-2.124	4.35900845
7021	7021	TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	-2.479	5.57510895
3866	3866	KRT15	keratin 15	-2.662	6.32909841
5764	5764	PTN	pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	-2.895	7.43843954
3075	3075	CFH	complement factor H	-2.949	7.7221362

Search Term	Gene Id	Symbol	Gene Name	logRatio MM minus PM	Fold Change
Gene up regulated in MM compared to PM					
6696	6696	SPP1	secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	1.797	3.47496874
4745	4745	NELL1	NEL-like 1 (chicken)	1.697	3.24226048
6192	6192	RPS4Y1	ribosomal protein S4, Y-linked 1	1.554	2.93630127
91353	91353	CTA-246H3.1	similar to omega protein	1.515	2.85798828
91316	91316	LOC91316	similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)	1.499	2.82646729
4256	4256	MGP	matrix Gla protein	1.392	2.62442251
216	216	ALDH1A1	aldehyde dehydrogenase 1 family, member A1	1.367	2.5793365
4111	4111	MAGEA12	melanoma antigen family A, 12	1.333	2.51925996
3426	3426	CFI	complement factor I	1.278	2.42502564
2947	2947	GSTM3	glutathione S-transferase M3 (brain)	1.262	2.39827983
23336	23336	DMN	desmuslin	1.247	2.3734736
12	12	SERPINA3	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	1.211	2.31498043
3485	3485	IGFBP2	insulin-like growth factor binding protein 2, 36kDa	1.206	2.30697121
3492	3492	IGH@	immunoglobulin heavy locus	1.191	2.28310941
6781	6781	STC1	stanniocalcin 1	1.157	2.22993244
730	730	C7	complement component 7	1.151	2.22067767
7422	7422	VEGFA	vascular endothelial growth factor A	1.14	2.20381023
4233	4233	MET	met proto-oncogene (hepatocyte growth factor receptor)	1.136	2.19770844
2138	2138	EYA1	eyes absent homolog 1 (Drosophila)	1.087	2.12431837
2335	2335	FN1	fibronectin 1	1.071	2.10088909
7991	7991	TUSC3	tumor suppressor candidate 3	1.044	2.06193664
5352	5352	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	1.038	2.05337909
7078	7078	TIMP3	TIMP metallopeptidase inhibitor 3 (Sorsby fundus dystrophy, pseudoinflammatory)	1.026	2.0363704
7018	7018	TF	transferrin	1.024	2.03354935
1E+05	114088	TRIM9	tripartite motif-containing 9	1.022	2.0307322
5740	5740	PTGIS	prostaglandin I2 (prostacyclin) synthase	1.002	2.00277451
Gene down regulated in MM compared to PM					
27065	27065	D4S234E	DNA segment on chromosome 4 (unique) 234 expressed sequence	-1.011	2.01530752
6283	6283	S100A12	S100 calcium binding protein A12	-1.013	2.01810327
2878	2878	GPX3	glutathione peroxidase 3 (plasma)	-1.017	2.0237064
7286	7286	TUFT1	tuftelin 1	-1.019	2.0265138
909	909	CD1A	CD1a molecule	-1.022	2.0307322
4155	4155	MBP	myelin basic protein	-1.024	2.03354935
445	445	ASS1	argininosuccinate synthetase 1	-1.027	2.03778239
11254	11254	SLC6A14	solute carrier family 6 (amino acid transporter), member 14	-1.028	2.03919537
23593	23593	HEBP2	heme binding protein 2	-1.033	2.04627494
26085	26085	KLK13	kallikrein-related peptidase 13	-1.033	2.04627494
3557	3557	IL1RN	interleukin 1 receptor antagonist	-1.036	2.05053448
55040	55040	EPN3	epsin 3	-1.037	2.05195629
306	306	ANXA3	annexin A3	-1.038	2.05337909
1E+05	131578	LRRC15	leucine rich repeat containing 15	-1.038	2.05337909
2707	2707	GJB3	gap junction protein, beta 3, 31kDa	-1.044	2.06193664
6401	6401	SELE	selectin E (endothelial adhesion molecule 1)	-1.048	2.06766147
55612	55612	C20orf42	chromosome 20 open reading frame 42	-1.051	2.07196553
3983	3983	ABLIM1	actin binding LIM protein 1	-1.062	2.08782385
563	563	AZGP1	alpha-2-glycoprotein 1, zinc-binding	-1.064	2.0907202
646	646	BNC1	basonuclin 1	-1.065	2.09216988
1646	1646	AKR1C2	aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III)	-1.065	2.09216988
3918	3918	LAMC2	laminin, gamma 2	-1.067	2.09507225
10276	10276	NET1	neuroepithelial cell transforming gene 1	-1.076	2.10818285
288	288	ANK3	ankyrin 3, node of Ranvier (ankyrin G)	-1.076	2.10818285
10850	10850	CCL27	chemokine (C-C motif) ligand 27	-1.077	2.10964463
4499	4499	MT1M	metallothionein 1M	-1.078	2.11110744
51458	51458	RHCG	Rh family, C glycoprotein	-1.08	2.11403608
1515	1515	CTSL2	cathepsin L2	-1.083	2.11843667
3117	3117	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	-1.085	2.12137548
6362	6362	CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-	-1.094	2.13465068

			regulated)		
80004	80004	RBM35B	RNA binding motif protein 35B	-1.097	2.13909418
51228	51228	GLTP	glycolipid transfer protein	-1.106	2.15248025
1040	1040	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1	-1.124	2.17950422
3909	3909	LAMA3	laminin, alpha 3	-1.129	2.18707091
202	202	AIM1	absent in melanoma 1	-1.132	2.19162353
5655	5655	KLK10	kallikrein-related peptidase 10	-1.134	2.19466388
9314	9314	KLF4	Kruppel-like factor 4 (gut)	-1.14	2.20381023
4856	4856	NOV	nephroblastoma overexpressed gene	-1.14	2.20381023
1359	1359	CPA3	carboxypeptidase A3 (mast cell)	-1.159	2.23302592
1718	1718	DHCR24	24-dehydrocholesterol reductase	-1.164	2.24077843
51200	51200	CPA4	carboxypeptidase A4	-1.176	2.25949443
1001	1001	CDH3	cadherin 3, type 1, P-cadherin (placental)	-1.199	2.29580483
11187	11187	PKP3	plakophilin 3	-1.201	2.2989897
242	242	ALOX12B	arachidonate 12-lipoxygenase, 12R type	-1.209	2.31177341
3934	3934	LCN2	lipocalin 2 (oncogene 24p3)	-1.211	2.31498043
222	222	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	-1.238	2.35871318
10974	10974	C10orf116	chromosome 10 open reading frame 116	-1.238	2.35871318
3120	3120	HLA-DQB2	major histocompatibility complex, class II, DQ beta 2	-1.245	2.37018554
53905	53905	DUOX1	dual oxidase 1	-1.256	2.38832637
8673	8673	VAMP8	vesicle-associated membrane protein 8 (endobrevin)	-1.258	2.39163959
6785	6785	ELOVL4	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 4	-1.265	2.4032721
1956	1956	EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	-1.265	2.4032721
25797	25797	QPCT	glutaminyl-peptide cyclotransferase (glutaminyl cyclase)	-1.268	2.40827476
1824	1824	DSC2	desmocollin 2	-1.273	2.41663569
8626	8626	TP73L	tumor protein p73-like	-1.281	2.43007358
771	771	CA12	carbonic anhydrase XII	-1.288	2.44189303
26154	26154	ABCA12	ATP-binding cassette, sub-family A (ABC1), member 12	-1.296	2.45547137
7851	7851	MALL	mal, T-cell differentiation protein-like	-1.303	2.46741434
6820	6820	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	-1.324	2.50359292
2261	2261	FGFR3	fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	-1.329	2.51228476
5646	5646	PRSS3	protease, serine, 3 (mesotrypsin)	-1.331	2.51576994
7051	7051	TGM1	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)	-1.338	2.5280062
80740	80740	LY6G6C	lymphocyte antigen 6 complex, locus G6C	-1.344	2.53854177
688	688	KLF5	Kruppel-like factor 5 (intestinal)	-1.35	2.54912125
7447	7447	VSNL1	visinin-like 1	-1.356	2.55974483
6286	6286	S100P	S100 calcium binding protein P	-1.374	2.59188193
57758	57758	SCUBE2	signal peptide, CUB domain, EGF-like 2	-1.4	2.63901582
5275	5275	SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	-1.404	2.64634288
4493	4493	MT1E	metallothionein 1E	-1.412	2.66105808
1634	1634	DCN	decorin	-1.414	2.66474965
3613	3613	IMPA2	inositol(myo)-1(or 4)-monophosphatase 2	-1.418	2.67214816
3898	3898	LAD1	ladinin 1	-1.419	2.67400099
6337	6337	SCNN1A	sodium channel, nonvoltage-gated 1 alpha	-1.427	2.68886999
1308	1308	COL17A1	collagen, type XVII, alpha 1	-1.427	2.68886999
760	760	CA2	carbonic anhydrase II	-1.431	2.69633546
5055	5055	SERPINB2	serpin peptidase inhibitor, clade B (ovalbumin), member 2	-1.454	2.73966596
5653	5653	KLK6	kallikrein-related peptidase 6	-1.466	2.7625489
7739	7739	ZNF185	zinc finger protein 185 (LIM domain)	-1.469	2.76829943
10653	10653	SPINT2	serine peptidase inhibitor, Kunitz type, 2	-1.473	2.77598544
2205	2205	FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	-1.474	2.77791027
79852	79852	ABHD9	abhydrolase domain containing 9	-1.481	2.79142153
999	999	CDH1	cadherin 1, type 1, E-cadherin (epithelial)	-1.513	2.85402901
3429	3429	IFI27	interferon, alpha-inducible protein 27	-1.566	2.9608266
8710	8710	SERPINB7	serpin peptidase inhibitor, clade B (ovalbumin), member 7	-1.57	2.96904714
9022	9022	CLIC3	chloride intracellular channel 3	-1.575	2.97935493
8424	8424	BBOX1	butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1	-1.591	3.01258093
25984	25984	KRT23	keratin 23 (histone deacetylase inducible)	-1.627	3.08870053
10874	10874	NMU	neuromedin U	-1.646	3.12964713
6382	6382	SDC1	syndecan 1	-1.652	3.14269007
79983	79983	POF1B	premature ovarian failure, 1B	-1.683	3.21094955
2697	2697	GJA1	gap junction protein, alpha 1, 43kDa	-1.691	3.2288043
23086	23086	EXPH5	exophilin 5	-1.691	3.2288043

3397	3397	ID1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	-1.703	3.25577274
57152	57152	SLURP1	secreted LY6/PLAUR domain containing 1	-1.71	3.27160823
3728	3728	JUP	junction plakoglobin	-1.759	3.38463439
7306	7306	TYRP1	tyrosinase-related protein 1	-1.766	3.40109664
822	822	CAPG	capping protein (actin filament), gelsolin-like	-1.769	3.40817638
1525	1525	CXADR	coxsackie virus and adenovirus receptor	-1.786	3.44857418
9890	9890	LPPR4	plasticity related gene 1	-1.789	3.45575275
11012	11012	KLK11	kallikrein-related peptidase 11	-1.797	3.47496874
4312	4312	MMP1	matrix metallopeptidase 1 (interstitial collagenase)	-1.831	3.55783597
667	667	DST	dystonin	-1.832	3.56030293
9982	9982	FGFBP1	fibroblast growth factor binding protein 1	-1.837	3.57266341
934	934	CD24	CD24 molecule	-1.859	3.62756132
7277	7277	TUBA4A	tubulin, alpha 4a	-1.862	3.63511247
8796	8796	SCEL	sciellin	-1.893	3.71406741
1E+05	113146	C14orf78	chromosome 14 open reading frame 78	-1.931	3.81319418
79755	79755	ZNF750	zinc finger protein 750	-1.951	3.86642439
1041	1041	CDSN	corneodesmosin	-1.964	3.90142185
57016	57016	AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	-2.013	4.03620654
57111	57111	RAB25	RAB25, member RAS oncogene family	-2.021	4.05865019
11202	11202	KLK8	kallikrein-related peptidase 8	-2.056	4.15831774
3858	3858	KRT10	keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	-2.096	4.27522396
1382	1382	CRABP2	cellular retinoic acid binding protein 2	-2.101	4.29006647
3815	3815	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	-2.11	4.31691295
1672	1672	DEFB1	defensin, beta 1	-2.173	4.50960165
25818	25818	KLK5	kallikrein-related peptidase 5	-2.201	4.59797939
3034	3034	HAL	histidine ammonia-lyase	-2.21	4.62675274
26239	26239	LCE2B	late cornified envelope 2B	-2.272	4.82992237
3866	3866	KRT15	keratin 15	-2.301	4.92799229
6590	6590	SLPI	secretory leukocyte peptidase inhibitor	-2.372	5.17658262
360	360	AQP3	aquaporin 3 (Gill blood group)	-2.386	5.22706102
64065	64065	PERP	PERP, TP53 apoptosis effector	-2.412	5.32211616
23650	23650	TRIM29	tripartite motif-containing 29	-2.425	5.37029001
5493	5493	PPL	periplakin	-2.488	5.609997
383	383	ARG1	arginase, liver	-2.522	5.74377804
57402	57402	S100A14	S100 calcium binding protein A14	-2.527	5.763719
5650	5650	KLK7	kallikrein-related peptidase 7	-2.552	5.86446703
4070	4070	TACSTD2	tumor-associated calcium signal transducer 2	-2.589	6.01681501
5266	5266	PI3	peptidase inhibitor 3, skin-derived (SKALP)	-2.618	6.13898438
84525	84525	HOP	homeodomain-only protein	-2.682	6.41744933
1825	1825	DSC3	desmocollin 3	-2.682	6.41744933
1474	1474	CST6	cystatin E/M	-2.69	6.45313407
810	810	CALML3	calmodulin-like 3	-2.698	6.48901724
27076	27076	LYPD3	LY6/PLAUR domain containing 3	-2.708	6.53415193
3849	3849	KRT2	keratin 2 (epidermal ichthyosis bullosa of Siemens)	-2.727	6.62077453
1830	1830	DSG3	desmoglein 3 (pemphigus vulgaris antigen)	-2.826	7.09105359
9635	9635	CLCA2	chloride channel, calcium activated, family member 2	-2.902	7.47461878
4014	4014	LOR	loricrin	-2.953	7.74357622
6317	6317	SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	-2.993	7.96127777
3713	3713	IVL	involucrin	-3.116	8.66980773
2810	2810	SFN	stratifin	-3.132	8.76649413
6318	6318	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	-3.147	8.85811668
1828	1828	DSG1	desmoglein 1	-3.177	9.04424454
9547	9547	CXCL14	chemokine (C-X-C motif) ligand 14	-3.24	9.44794129
51806	51806	CALML5	calmodulin-like 5	-3.451	10.9358996
1832	1832	DSP	desmoplakin	-3.469	11.0731977
1823	1823	DSC1	desmocollin 1	-3.491	11.2433496
3868	3868	KRT16	keratin 16 (focal non-epidermolytic palmoplantar keratoderma)	-3.564	11.8268995
11005	11005	SPINK5	serine peptidase inhibitor, Kazal type 5	-3.587	12.0169594
6280	6280	S100A9	S100 calcium binding protein A9	-3.629	12.3719414
1475	1475	CSTA	cystatin A (stefin A)	-3.647	12.5272687
6698	6698	SPRR1A	small proline-rich protein 1A	-3.774	13.6800348
3872	3872	KRT17	keratin 17	-3.966	15.6273365
6273	6273	S100A2	S100 calcium binding protein A2	-4.102	17.1721646
5268	5268	SERPINB5	serpin peptidase inhibitor, clade B (ovalbumin), member 5	-4.134	17.557311
3852	3852	KRT5	keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types)	-4.462	22.0392007

3854	3854	KRT6B	keratin 6B	-4.663	25.3339477
3848	3848	KRT1	keratin 1 (epidermolytic hyperkeratosis)	-4.865	29.1414347
6699	6699	SPRR1B	small proline-rich protein 1B (cornifin)	-4.865	29.1414347
6279	6279	S100A8	S100 calcium binding protein A8	-4.928	30.4421848
3853	3853	KRT6A	keratin 6A	-4.965	31.2330163
3861	3861	KRT14	keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner)	-5.868	58.4041913

Search Term	Gene ID	Gene Symbol	Gene Name	Log Ratio MM minus MN	Fold Change
Gene up regulated in MM compared to MN					
6696	6696	SPP1	Secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	4.612	24.4540243
23532	23532	PRAME	Preferentially expressed antigen in melanoma	3.907	15.0011375
-1	-1	N.N.		3.574	11.909162
91316	91316	LOC91316	Similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)	3.328	10.0421759
91353	91353	CTA-246H3.1	Similar to omega protein	3.2	9.18958684
2335	2335	FN1	Fibronectin 1	3.173	9.0192033
3492	3492	IGH@		2.976	7.86801659
7453	7453	WARS	Tryptophanyl-tRNA synthetase	2.921	7.57370905
221692	221692	PHACTR1	Phosphatase and actin regulator 1	2.807	6.99827812
10537	10537	UBD	Ubiquitin D	2.722	6.59786839
9518	9518	GDF15	Growth differentiation factor 15	2.645	6.25495715
2	2	A2M	Alpha-2-macroglobulin	2.639	6.22899753
713	713	C1QB	Complement component 1, q subcomponent, B chain	2.486	5.60222528
4111	4111	MAGEA12	Melanoma antigen family A, 12	2.46	5.50216727
4283	4283	CXCL9	Chemokine (C-X-C motif) ligand 9	2.329	5.02456952
12	12	SERPINA3	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	2.31	4.9588308
5996	5996	RGS1	Regulator of G-protein signaling 1	2.253	4.7667303
3512	3512	IGJ	Immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	2.243	4.73380409
712	712	C1QA	Complement component 1, q subcomponent, A chain	2.102	4.29304115
51303	51303	FKBP11	FK506 binding protein 11, 19 kDa	2.079	4.2251425
6035	6035	RNASE1	Ribonuclease, RNase A family, 1 (pancreatic)	2.062	4.17564771
4435	4435	CITED1	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1	1.967	3.90954307
3627	3627	CXCL10	Chemokine (C-X-C motif) ligand 10	1.934	3.82113175
4162	4162	MCAM	Melanoma cell adhesion molecule	1.907	3.75028439
597	597	BCL2A1	BCL2-related protein A1	1.899	3.72954595
344	344	APOC2	Apolipoprotein C-II	1.873	3.66293475
7076	7076	TIMP1	TIMP metallopeptidase inhibitor 1	1.839	3.57761961
10563	10563	CXCL13	Chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)	1.827	3.54798522
7852	7852	CXCR4	Chemokine (C-X-C motif) receptor 4	1.822	3.53571012
55872	55872	PBK	PDZ binding kinase	1.803	3.48945082
4311	4311	MME	Membrane metallo-endopeptidase	1.763	3.39403161
3426	3426	CFI	Complement factor I	1.757	3.37994554
10763	10763	NES	Nestin	1.746	3.35427274
1282	1282	COL4A1	Collagen, type IV, alpha 1	1.724	3.30351066
5327	5327	PLAT	Plasminogen activator, tissue	1.712	3.27614679
4318	4318	MMP9	Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	1.706	3.26254997
929	929	CD14	CD14 molecule	1.698	3.24450862
11065	11065	UBE2C	Ubiquitin-conjugating enzyme E2C	1.654	3.14704978
3485	3485	IGFBP2	Insulin-like growth factor binding protein 2, 36kDa	1.647	3.13181719
6241	6241	RRM2	Ribonucleotide reductase M2 polypeptide	1.641	3.11881937
1284	1284	COL4A2	Collagen, type IV, alpha 2	1.633	3.10157283
51514	51514	DTL	Denticleless homolog (Drosophila)	1.633	3.10157283
9232	9232	PTTG1	Pituitary tumor-transforming 1	1.632	3.09942372
10437	10437	IFI30	Interferon, gamma-inducible protein 30	1.622	3.07801444
4100	4100	MAGEA1	Melanoma antigen family A, 1 (directs expression of antigen MZ2-E)	1.599	3.02933263
2207	2207	FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	1.589	3.0084075
813	813	CALU	Calumenin	1.588	3.00632296
7805	7805	LAPTM5	Lysosomal associated multispanning membrane protein 5	1.568	2.96493402
10788	10788	IQGAP2	IQ motif containing GTPase activating protein 2	1.564	2.95672486

6574	6574	SLC20A1	Solute carrier family 20 (phosphate transporter), member 1	1.563	2.95467613
3838	3838	KPNA2	Karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	1.546	2.92006402
27242	27242	TNFRSF21	Tumor necrosis factor receptor superfamily, member 21	1.531	2.8898608
1164	1164	CKS2	CDC28 protein kinase regulatory subunit 2	1.52	2.8679105
10112	10112	KIF20A	Kinesin family member 20A	1.519	2.8659233
7422	7422	VEGFA	Vascular endothelial growth factor A	1.518	2.86393748
7298	7298	TYMS	Thymidylate synthetase	1.514	2.85600796
11015	11015	KDELR3		1.504	2.83628007
9787	9787	DLG7	Discs, large homolog 7 (Drosophila)	1.491	2.8108374
684	684	BST2	Bone marrow stromal cell antigen 2	1.479	2.78755448
22974	22974	TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	1.479	2.78755448
6515	6515	SLC2A3	Solute carrier family 2 (facilitated glucose transporter), member 3	1.476	2.78176394
11145	11145	HRASLS3	HRAS-like suppressor 3	1.468	2.76638126
891	891	CCNB1	Cyclin B1	1.467	2.76446441
9133	9133	CCNB2	Cyclin B2	1.464	2.75872184
4745	4745	NELL1	NEL-like 1 (chicken)	1.447	2.72640521
4233	4233	MET	Met proto-oncogene (hepatocyte growth factor receptor)	1.44	2.71320865
23643	23643	LY96	Lymphocyte antigen 96	1.437	2.70757256
9332	9332	CD163	CD163 molecule	1.433	2.70007597
4256	4256	MGP	Matrix Gla protein	1.432	2.69820507
6271	6271	S100A1	S100 calcium binding protein A1	1.428	2.69073442
9123	9123	SLC16A3	Solute carrier family 16, member 3 (monocarboxylic acid transporter 4)	1.42	2.67585511
4837	4837	NNMT	Nicotinamide N-methyltransferase	1.414	2.66474965
7262	7262	PHLDA2	Pleckstrin homology-like domain, family A, member 2	1.412	2.66105808
9768	9768	KIAA0101	KIAA0101	1.403	2.64450921
5450	5450	POU2AF1	POU class 2 associating factor 1	1.396	2.63170905
1687	1687	DFNA5	Deafness, autosomal dominant 5	1.384	2.6099099
963	963	CD53	CD53 molecule	1.379	2.60088029
6772	6772	STAT1	Signal transducer and activator of transcription 1, 91kDa	1.368	2.58112498
397	397	ARHGDIB	Rho GDP dissociation inhibitor (GDI) beta	1.366	2.57754926
7037	7037	TFRC	Transferrin receptor (p90, CD71)	1.354	2.55619873
57103	57103	C12orf5	Chromosome 12 open reading frame 5	1.353	2.55442752
2026	2026	ENO2	Enolase 2 (gamma, neuronal)	1.35	2.54912125
3576	3576	IL8	Interleukin 8	1.35	2.54912125
4321	4321	MMP12	Matrix metallopeptidase 12 (macrophage elastase)	1.348	2.54558987
5351	5351	PLOD1	Procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1	1.346	2.54206338
63915	63915	MUTED		1.337	2.52625452
81575	81575	APOLD1	Apolipoprotein L domain containing 1	1.329	2.51228476
2138	2138	EYA1	Eyes absent homolog 1 (Drosophila)	1.324	2.50359292
94239	94239	H2AFV	H2A histone family, member V	1.32	2.4966611
2633	2633	GBP1	Guanylate binding protein 1, interferon-inducible, 67kDa	1.317	2.49147483
5265	5265	SERPINA1	Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	1.317	2.49147483
5329	5329	PLAUR	Plasminogen activator, urokinase receptor	1.316	2.48974847
1063	1063	CENPF	Centromere protein F, 350/400ka (mitosin)	1.315	2.48802331
7980	7980	TFPI2	Tissue factor pathway inhibitor 2	1.314	2.48629934
9500	9500	MAGED1	Melanoma antigen family D, 1	1.312	2.48285498
871	871	SERPINH1	Serpin peptidase inhibitor, clade H (heat shock protein 47), member 1, (collagen binding protein 1)	1.298	2.45887773
7052	7052	TGM2	Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	1.296	2.45547137
3937	3937	LCP2	Lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	1.294	2.45206972
2181	2181	ACSL3	Acyl-CoA synthetase long-chain family member 3	1.292	2.44867278
6790	6790	AURKA	Aurora kinase A	1.287	2.44020102
5920	5920	RARRES3	Retinoic acid receptor responder (tazarotene induced) 3	1.286	2.43851019
51338	51338	MS4A4A	Membrane-spanning 4-domains, subfamily A, member 4	1.281	2.43007358
7545	7545	ZIC1	Zic family member 1 (odd-paired homolog, Drosophila)	1.28	2.42838977
10019	10019	SH2B3	SH2B adaptor protein 3	1.278	2.42502564
11326	11326	VSIG4	V-set and immunoglobulin domain containing 4	1.278	2.42502564
55379	55379	LRRC59	Leucine rich repeat containing 59	1.278	2.42502564
9833	9833	MELK	Maternal embryonic leucine zipper kinase	1.277	2.42334532
23327	23327	NEDD4L	Neural precursor cell expressed, developmentally down-regulated 4-like	1.27	2.41161566
28959	28959	TMEM176B	Transmembrane protein 176B	1.263	2.39994276
1033	1033	CDKN3	Cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase)	1.26	2.39495741

3006	3006	HIST1H1C	Histone cluster 1, H1c	1.254	2.38501774
23406	23406	COTL1	Coactosin-like 1 (Dictyostelium)	1.253	2.38336515
6781	6781	STC1	Stanniocalcin 1	1.25	2.37841423
7153	7153	TOP2A	Topoisomerase (DNA) II alpha 170kDa	1.25	2.37841423
3669	3669	ISG20	Interferon stimulated exonuclease gene 20kDa	1.245	2.37018554
142	142	PARP1	Poly (ADP-ribose) polymerase family, member 1	1.243	2.36690204
7378	7378	UPP1	Uridine phosphorylase 1	1.235	2.35381347
991	991	CDC20	Cell division cycle 20 homolog (S. cerevisiae)	1.232	2.34892394
6745	6745	SSR1	Signal sequence receptor, alpha (translocon-associated protein alpha)	1.231	2.34729636
6352	6352	CCL5	Chemokine (C-C motif) ligand 5	1.23	2.3456699
23516	23516	SLC39A14	Solute carrier family 39 (zinc transporter), member 14	1.224	2.33593479
29887	29887	SNX10	Sorting nexin 10	1.224	2.33593479
3959	3959	LGALS3BP	Lectin, galactoside-binding, soluble, 3 binding protein	1.222	2.33269874
10095	10095	ARPC1B	Actin related protein 2/3 complex, subunit 1B, 41kDa	1.219	2.32785307
7305	7305	TYROBP	TYRO protein tyrosine kinase binding protein	1.211	2.31498043
116372	116372	LYPD1	LY6/PLAUR domain containing 1	1.211	2.31498043
8091	8091	HMGA2	High mobility group AT-hook 2	1.21	2.31337637
10486	10486	CAP2	CAP, adenylate cyclase-associated protein, 2 (yeast)	1.209	2.31177341
1601	1601	DAB2	Disabled homolog 2, mitogen-responsive phosphoprotein (Drosophila)	1.206	2.30697121
5577	5577	PRKAR2B	Protein kinase, cAMP-dependent, regulatory, type II, beta	1.206	2.30697121
9055	9055	PRC1	Protein regulator of cytokinesis 1	1.203	2.30217898
23213	23213	SULF1	Sulfatase 1	1.198	2.29421405
10211	10211	FLOT1	Flotillin 1	1.196	2.2910358
87	87	ACTN1	Actinin, alpha 1	1.193	2.28627667
1846	1846	DUSP4	Dual specificity phosphatase 4	1.191	2.28310941
3371	3371	TNC	Tenascin C (hexabrachion)	1.189	2.27994655
6876	6876	TAGLN	Transgelin	1.179	2.2641978
27299	27299	ADAMDEC1	ADAM-like, decysin 1	1.178	2.26262893
8406	8406	SRPX	Sushi-repeat-containing protein, X-linked	1.174	2.25636427
1508	1508	CTSB	Cathepsin B	1.173	2.25480082
6402	6402	SELL	Selectin L (lymphocyte adhesion molecule 1)	1.173	2.25480082
6947	6947	TCN1	Transcobalamin I (vitamin B12 binding protein, R binder family)	1.167	2.24544284
3357	3357	HTR2B	5-hydroxytryptamine (serotonin) receptor 2B	1.166	2.24388696
5476	5476	CTSA	Cathepsin A	1.166	2.24388696
5352	5352	PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	1.165	2.24233216
962	962	CD48	CD48 molecule	1.15	2.21913894
3491	3491	CYR61	Cysteine-rich, angiogenic inducer, 61	1.149	2.21760129
11014	11014	KDELR2	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2	1.149	2.21760129
717	717	C2	Complement component 2	1.136	2.19770844
5698	5698	PSMB9	Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	1.131	2.19010494
4017	4017	LOXL2	Lysyl oxidase-like 2	1.127	2.18404109
9928	9928	KIF14	Kinesin family member 14	1.123	2.17799403
10656	10656	KHDRBS3	KH domain containing, RNA binding, signal transduction associated 3	1.123	2.17799403
1978	1978	EIF4EBP1	Eukaryotic translation initiation factor 4E binding protein 1	1.122	2.17648488
2020	2020	EN2	Engrailed homeobox 2	1.122	2.17648488
11004	11004	KIF2C	Kinesin family member 2C	1.119	2.17196371
51203	51203	NUSAP1	Nucleolar and spindle associated protein 1	1.114	2.16444929
2258	2258	FGF13	Fibroblast growth factor 13	1.111	2.15995312
3108	3108	HLA-DMA	Major histocompatibility complex, class II, DM alpha	1.109	2.15696086
3689	3689	ITGB2	Integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	1.106	2.15248025
6351	6351	CCL4	Chemokine (C-C motif) ligand 4	1.105	2.15098878
7018	7018	TF	Transferrin	1.105	2.15098878
4104	4104	MAGEA5	Melanoma antigen family A, 5	1.103	2.14800894
719	719	C3AR1	Complement component 3a receptor 1	1.102	2.14652057
6347	6347	CCL2	Chemokine (C-C motif) ligand 2	1.102	2.14652057
4085	4085	MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	1.1	2.14354693
6999	6999	TDO2	Tryptophan 2,3-dioxygenase	1.099	2.14206165
64092	64092	SAMSN1	SAM domain, SH3 domain and nuclear localization signals 1	1.098	2.1405774
3383	3383	ICAM1	Intercellular adhesion molecule 1 (CD54), human rhinovirus receptor	1.096	2.13761198
701	701	BUB1B	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	1.095	2.13613082
6891	6891	TAP2	Transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	1.094	2.13465068

58986	58986	TMEM8	Transmembrane protein 8 (five membrane-spanning domains)	1.094	2.13465068
8836	8836	GGH	Gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	1.093	2.13317156
10954	10954	PDIA5	Protein disulfide isomerase family A, member 5	1.093	2.13317156
85236	85236	HIST1H2BK	Histone cluster 1, H2bk	1.092	2.13169347
3059	3059	HCLS1	Hematopoietic cell-specific Lyn substrate 1	1.09	2.12874036
5315	5315	PKM2	Pyruvate kinase, muscle	1.09	2.12874036
3017	3017	HIST1H2BD	Histone cluster 1, H2bd	1.085	2.12137548
5272	5272	SERPINB9	Serpin peptidase inhibitor, clade B (ovalbumin), member 9	1.085	2.12137548
7184	7184	HSP90B1	Heat shock protein 90kDa beta (Grp94), member 1	1.085	2.12137548
9404	9404	LPXN	Leupaxin	1.083	2.11843667
7351	7351	UCP2	Uncoupling protein 2 (mitochondrial, proton carrier)	1.082	2.11696879
8905	8905	AP1S2	Adaptor-related protein complex 1, sigma 2 subunit	1.082	2.11696879
165	165	AEBP1	AE binding protein 1	1.08	2.11403608
4811	4811	NID1	Nidogen 1	1.078	2.11110744
6890	6890	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	1.073	2.10380356
10440	10440	TIMM17A	Translocase of inner mitochondrial membrane 17 homolog A (yeast)	1.073	2.10380356
5721	5721	PSME2	Proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	1.071	2.10088909
1462	1462	VCAN	Versican	1.067	2.09507225
3099	3099	HK2	Hexokinase 2	1.066	2.09362056
23194	23194	FBXL7	F-box and leucine-rich repeat protein 7	1.066	2.09362056
5690	5690	PSMB2	Proteasome (prosome, macropain) subunit, beta type, 2	1.064	2.0907202
23484	23484	LEPROTL1	Leptin receptor overlapping transcript-like 1	1.064	2.0907202
149111	149111	CNIH3	Cornichon homolog 3 (Drosophila)	1.064	2.0907202
7077	7077	TIMP2	TIMP metallopeptidase inhibitor 2	1.062	2.08782385
533	533	ATP6V0B	ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b	1.057	2.08060053
50515	50515	CHST11	Carbohydrate (chondroitin 4) sulfotransferase 11	1.057	2.08060053
54828	54828	BCAS3	Breast carcinoma amplified sequence 3	1.057	2.08060053
9263	9263	STK17A	Serine/threonine kinase 17a	1.053	2.07483987
3620	3620	INDO	Indoleamine-pyrrole 2,3 dioxygenase	1.05	2.07052985
54927	54927	CHCHD3	Coiled-coil-helix-coiled-coil-helix domain containing 3	1.049	2.06909516
60481	60481	ELOVL5	ELOVL family member 5, elongation of long chain fatty acids (FEN1/Elo2, SUR4/Elo3-like, yeast)	1.049	2.06909516
6782	6782	STCH	Stress 70 protein chaperone, microsome-associated, 60kDa	1.048	2.06766147
79801	79801	SHCBP1	SHC SH2-domain binding protein 1	1.048	2.06766147
10460	10460	TACC3	Transforming, acidic coiled-coil containing protein 3	1.047	2.06622878
23530	23530	NNT	Nicotinamide nucleotide transhydrogenase	1.047	2.06622878
983	983	CDC2	Cell division cycle 2, G1 to S and G2 to M	1.037	2.05195629
50999	50999	TMED5	Transmembrane emp24 protein transport domain containing 5	1.036	2.05053448
55647	55647	RAB20	RAB20, member RAS oncogene family	1.036	2.05053448
2305	2305	FOXM1	Forkhead box M1	1.034	2.0476938
9212	9212	AURKB	Aurora kinase B	1.034	2.0476938
29028	29028	ATAD2	ATPase family, AAA domain containing 2	1.033	2.04627494
8934	8934	RAB7L1	RAB7, member RAS oncogene family-like 1	1.032	2.04485706
256227	256227	MGC87042	Similar to Six transmembrane epithelial antigen of prostate	1.029	2.04060932
64151	64151	NCAPG	Non-SMC condensin I complex, subunit G	1.026	2.0363704
5641	5641	LGMN	Legumain	1.025	2.03495938
3074	3074	HEXB	Hexosaminidase B (beta polypeptide)	1.021	2.02932509
332	332	BIRC5	Baculoviral IAP repeat-containing 5 (survivin)	1.019	2.0265138
1503	1503	CTPS	CTP synthase	1.018	2.02510961
9447	9447	AIM2	Absent in melanoma 2	1.017	2.0237064
914	914	CD2	CD2 molecule	1.014	2.0195026
11013	11013	TMSL8	Thymosin-like 8	1.013	2.01810327
50486	50486	G0S2	G0/G1switch 2	1.012	2.01670491
5230	5230	PGK1	Phosphoglycerate kinase 1	1.01	2.0139111
6185	6185	RPN2	Ribophorin II	1.009	2.01251565
528	528	ATP6V1C1	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C1	1.008	2.01112116
3309	3309	HSPA5	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	1.006	2.00833509
4192	4192	MDK	Midkine (neurite growth-promoting factor 2)	1.005	2.0069435
728	728	C5AR1	Complement component 5a receptor 1	1.003	2.00416321
1020	1020	CDK5	Cyclin-dependent kinase 5	1.002	2.00277451
5696	5696	PSMB8	Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	1.002	2.00277451
10384	10384	BTN3A3	Butyrophilin, subfamily 3, member A3	1.002	2.00277451
7873	7873	ARMET	Arginine-rich, mutated in early stage tumors	1.001	2.00138677
23753	23753	SDF2L1	Stromal cell-derived factor 2-like 1	1.001	2.00138677

Gene down regulated in MM compared to MN					
6136	6136	RPL12	Ribosomal protein L12	-1	2
7001	7001	PRDX2	Peroxiredoxin 2	-1	2
59338	59338	PLEKHA1	Pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 1	-1.002	2.00277451
170680	170680	PSORS1C2	Psoriasis susceptibility 1 candidate 2	-1.003	2.00416321
116039	116039	OSR2	Odd-skipped related 2 (Drosophila)	-1.004	2.00555287
6261	6261	RYR1	Ryanodine receptor 1 (skeletal)	-1.006	2.00833509
55214	55214	LEPREL1	Leprecan-like 1	-1.006	2.00833509
79056	79056	PRRG4	Proline rich Gla (G-carboxyglutamic acid) 4 (transmembrane)	-1.008	2.01112116
1294	1294	COL7A1	Collagen, type VII, alpha 1 (epidermolysis bullosa, dystrophic, dominant and recessive)	-1.009	2.01251565
56288	56288	PARD3	Par-3 partitioning defective 3 homolog (C. elegans)	-1.012	2.01670491
60495	60495	HPSE2	Heparanase 2	-1.013	2.01810327
9651	9651	PLCH2	Phospholipase C, eta 2	-1.014	2.0195026
9796	9796	PHYHIP	Phytanoyl-CoA 2-hydroxylase interacting protein	-1.015	2.02090289
51232	51232	CRIM1	Cysteine rich transmembrane BMP regulator 1 (chordin-like)	-1.02	2.02791896
3557	3557	IL1RN	Interleukin 1 receptor antagonist	-1.021	2.02932509
10924	10924	SMPDL3A	Sphingomyelin phosphodiesterase, acid-like 3A	-1.021	2.02932509
80303	80303	EFHD1	EF-hand domain family, member D1	-1.021	2.02932509
23461	23461	ABCA5	ATP-binding cassette, sub-family A (ABC1), member 5	-1.023	2.03214029
23259	23259	DDHD2	DDHD domain containing 2	-1.025	2.03495938
1638	1638	DCT	Dopachrome tautomerase (dopachrome delta-isomerase, tyrosine-related protein 2)	-1.027	2.03778239
7162	7162	TPBG	Trophoblast glycoprotein	-1.027	2.03778239
10602	10602	CDC42EP3	CDC42 effector protein (Rho GTPase binding) 3	-1.027	2.03778239
55040	55040	EPN3	Epsin 3	-1.028	2.03919537
3119	3119	HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	-1.029	2.04060932
2152	2152	F3	Coagulation factor III (thromboplastin, tissue factor)	-1.035	2.04911365
10810	10810	WASF3	WAS protein family, member 3	-1.038	2.05337909
5603	5603	MAPK13	Mitogen-activated protein kinase 13	-1.04	2.05622765
4692	4692	NDN	Necdin homolog (mouse)	-1.043	2.06050791
9414	9414	TJP2	Tight junction protein 2 (zona occludens 2)	-1.05	2.07052985
1028	1028	CDKN1C	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	-1.053	2.07483987
5126	5126	PCSK2	Proprotein convertase subtilisin/kexin type 2	-1.054	2.07627854
1842	1842	ECM2	Extracellular matrix protein 2, female organ and adipocyte specific	-1.058	2.0820432
3655	3655	ITGA6	Integrin, alpha 6	-1.06	2.08493152
4897	4897	NRCAM	Neuronal cell adhesion molecule	-1.062	2.08782385
23189	23189	ANKRD15	Ankyrin repeat domain 15	-1.063	2.08927153
928	928	CD9	CD9 molecule	-1.065	2.09216988
4675	4675	NAP1L3	Nucleosome assembly protein 1-like 3	-1.065	2.09216988
5652	5652	PRSS8	Protease, serine, 8	-1.066	2.09362056
51309	51309	ARMCX1	Armadillo repeat containing, X-linked 1	-1.067	2.09507225
91851	91851	CHRDL1	Chordin-like 1	-1.071	2.10088909
57146	57146	TMEM159	Transmembrane protein 159	-1.072	2.10234582
1124	1124	CHN2	Chimerin (chimaerin) 2	-1.075	2.10672207
1906	1906	EDN1	Endothelin 1	-1.077	2.10964463
4086	4086	SMAD1	SMAD family member 1	-1.077	2.10964463
1808	1808	DPYSL2	Dihydropyrimidinase-like 2	-1.084	2.11990557
4128	4128	MAOA	Monoamine oxidase A	-1.084	2.11990557
85458	85458	DIXDC1	DIX domain containing 1	-1.084	2.11990557
154	154	ADRB2	Adrenergic, beta-2-, receptor, surface	-1.087	2.12431837
1515	1515	CTSL2	Cathepsin L2	-1.089	2.12726535
7503	7503	XIST	X (inactive)-specific transcript	-1.09	2.12874036
288	288	ANK3	Ankyrin 3, node of Ranvier (ankyrin G)	-1.091	2.13021641
3918	3918	LAMC2	Laminin, gamma 2	-1.091	2.13021641
3769	3769	KCNJ13	Potassium inwardly-rectifying channel, subfamily J, member 13	-1.093	2.13317156
80206	80206	FHOD3	Formin homology 2 domain containing 3	-1.1	2.14354693
57758	57758	SCUBE2	Signal peptide, CUB domain, EGF-like 2	-1.104	2.14949835
11211	11211	FZD10	Frizzled homolog 10 (Drosophila)	-1.105	2.15098878
25976	25976	TIPARP	TCDD-inducible poly(ADP-ribose) polymerase	-1.108	2.15546629
3205	3205	HOXA9	Homeobox A9	-1.111	2.15995312
6509	6509	SLC1A4	Solute carrier family 1 (glutamate/neutral amino acid transporter), member 4	-1.111	2.15995312
55227	55227	LRRC1	Leucine rich repeat containing 1	-1.111	2.15995312
6280	6280	S100A9	S100 calcium binding protein A9	-1.112	2.1614508
6665	6665	SOX15	SRY (sex determining region Y)-box 15	-1.112	2.1614508

738	738	C11orf2	Chromosome 11 open reading frame2	-1.115	2.16595009
10351	10351	ABCA8	ATP-binding cassette, sub-family A (ABC1), member 8	-1.117	2.16895482
25878	25878	MXRA5	Matrix-remodelling associated 5	-1.118	2.17045874
2150	2150	F2RL1	Coagulation factor II (thrombin) receptor-like 1	-1.121	2.17497678
1580	1580	CYP4B1	Cytochrome P450, family 4, subfamily B, polypeptide 1	-1.122	2.17648488
79686	79686	C14orf139	Chromosome 14 open reading frame 139	-1.122	2.17648488
1646	1646	AKR1C2	Aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III)	-1.123	2.17799403
6662	6662	SOX9	SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal)	-1.126	2.18252775
10278	10278	EFS	Embryonal Fyn-associated substrate	-1.126	2.18252775
5349	5349	FXYD3	FXYD domain containing ion transport regulator 3	-1.127	2.18404109
23382	23382	KIAA0828	Adenosylhomocysteinase 3	-1.127	2.18404109
2013	2013	EMP2	Epithelial membrane protein 2	-1.129	2.18707091
55107	55107	TMEM16A	Transmembrane protein 16A	-1.129	2.18707091
2069	2069	EREG	Epiregulin	-1.13	2.1885874
283638	283638	KIAA0284	KIAA0284	-1.132	2.19162353
1153	1153	CIRBP	Cold inducible RNA binding protein	-1.133	2.19314318
5792	5792	PTPRF	Protein tyrosine phosphatase, receptor type, F	-1.133	2.19314318
55294	55294	FBXW7	F-box and WD repeat domain containing 7	-1.136	2.19770844
26298	26298	EHF	Ets homologous factor	-1.138	2.20075722
23002	23002	DAAM1	Dishevelled associated activator of morphogenesis 1	-1.141	2.20533833
1359	1359	CPA3	Carboxypeptidase A3 (mast cell)	-1.144	2.20992897
23242	23242	COBL	Cordon-bleu homolog (mouse)	-1.146	2.21299471
242	242	ALOX12B	Arachidonate 12-lipoxygenase, 12R type	-1.151	2.22067767
2941	2941	GSTA4	Glutathione S-transferase A4	-1.152	2.22221746
51090	51090	PLLP	Plasma membrane proteolipid (plasmolipin)	-1.155	2.22684324
11075	11075	STMN2	Stathmin-like 2	-1.156	2.2283873
23593	23593	HEBP2	Heme binding protein 2	-1.156	2.2283873
26330	26330	GAPDHS	Glyceraldehyde-3-phosphate dehydrogenase, spermatogenic	-1.158	2.23147864
694	694	BTG1	B-cell translocation gene 1, anti-proliferative	-1.16	2.23457428
9413	9413	C9orf61	Chromosome 9 open reading frame 61	-1.16	2.23457428
2770	2770	GNAI1	Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1	-1.161	2.2361237
26018	26018	LRIG1	Leucine-rich repeats and immunoglobulin-like domains 1	-1.161	2.2361237
4915	4915	NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	-1.163	2.23922578
7056	7056	THBD	Thrombomodulin	-1.168	2.24699981
6513	6513	SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	-1.173	2.25480082
3590	3590	IL11RA	Interleukin 11 receptor, alpha	-1.174	2.25636427
29091	29091	STXBP6	Syntaxin binding protein 6 (amisyn)	-1.175	2.25792881
2153	2153	F5	Coagulation factor V (proaccelerin, labile factor)	-1.176	2.25949443
2709	2709	GJB5	Gap junction protein, beta 5, 31.1kDa	-1.178	2.26262893
3816	3816	KLK1	Kallikrein 1	-1.178	2.26262893
3775	3775	KCNK1	Potassium channel, subfamily K, member 1	-1.18	2.26576777
7022	7022	TFAP2C	Transcription factor AP-2 gamma (activating enhancer binding protein 2 gamma)	-1.184	2.27205853
25854	25854	DKFZP564J102	Family with sequence similarity 149, member A	-1.185	2.27363395
23015	23015	GOLGA8A	Golgi autoantigen, golgin subfamily a, 8A	-1.187	2.27678806
10579	10579	TACC2	Transforming, acidic coiled-coil containing protein 2	-1.188	2.27836675
3248	3248	HPGD	Hydroxyprostaglandin dehydrogenase 15-(NAD)	-1.189	2.27994655
6137	6137	RPL13	Ribosomal protein L13	-1.189	2.27994655
6385	6385	SDC4	Syndecan 4	-1.195	2.28944832
1112	1112	CHES1	Forkhead box N3	-1.196	2.2910358
390	390	RND3	Rho family GTPase 3	-1.2	2.29739671
2202	2202	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	-1.201	2.2989897
26154	26154	ABCA12	ATP-binding cassette, sub-family A (ABC1), member 12	-1.202	2.30058379
79850	79850	FAM57A	Family with sequence similarity 57, member A	-1.203	2.30217898
9891	9891	NUAK1	NUAK family, SNF1-like kinase, 1	-1.206	2.30697121
2196	2196	FAT2	FAT tumor suppressor homolog 2 (Drosophila)	-1.209	2.31177341
56998	56998	CTNNBIP1	Catenin, beta interacting protein 1	-1.209	2.31177341
2114	2114	ETS2	V-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	-1.212	2.31658561
117247	117247	SLC16A10	Solute carrier family 16, member 10 (aromatic amino acid transporter)	-1.212	2.31658561
25875	25875	LETMD1	LETM1 domain containing 1	-1.214	2.31979931
4610	4610	MYCL1	V-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	-1.215	2.32140783
53335	53335	BCL11A	B-cell CLL/lymphoma 11A (zinc finger protein)	-1.216	2.32301746

5593	5593	PRKG2	Protein kinase, cGMP-dependent, type II	-1.217	2.32462822
1050	1050	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	-1.22	2.32946717
7088	7088	TLE1	Transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	-1.22	2.32946717
3400	3400	ID4	Inhibitor of DNA binding 4, dominant negative helix-loop-helix protein	-1.224	2.33593479
4477	4477	MSMB	Microseminoprotein, beta-	-1.231	2.34729636
6692	6692	SPINT1	Serine peptidase inhibitor, Kunitz type 1	-1.231	2.34729636
396	396	ARHGDIA	Rho GDP dissociation inhibitor (GDI) alpha	-1.234	2.3521825
3480	3480	IGF1R	Insulin-like growth factor 1 receptor	-1.234	2.3521825
4147	4147	MATN2	Matrilin 2	-1.235	2.35381347
51228	51228	GLTP	Glycolipid transfer protein	-1.236	2.35544558
2125	2125	EVPL	Envoplakin	-1.237	2.35707882
23150	23150	FRMD4B	FERM domain containing 4B	-1.237	2.35707882
9194	9194	SLC16A7	Solute carrier family 16, member 7 (monocarboxylic acid transporter 2)	-1.238	2.35871318
10391	10391	CORO2B	Coronin, actin binding protein, 2B	-1.243	2.36690204
1902	1902	EDG2	Endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2	-1.25	2.37841423
11341	11341	SCRG1	Scrapie responsive protein 1	-1.252	2.3817137
26053	26053	AUTS2	Autism susceptibility candidate 2	-1.256	2.38832637
5453	5453	POU3F1	POU class 3 homeobox 1	-1.257	2.38998241
1645	1645	AKR1C1	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	-1.258	2.39163959
1944	1944	EFNA3	Ephrin-A3	-1.26	2.39495741
10512	10512	SEMA3C	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	-1.26	2.39495741
3080	3080	CFHR2	Complement factor H-related 2	-1.262	2.39827983
10529	10529	NEBL	Nebulette	-1.262	2.39827983
79977	79977	GRHL2	Grainyhead-like 2 (Drosophila)	-1.262	2.39827983
53832	53832	IL20RA	Interleukin 20 receptor, alpha	-1.268	2.40827476
9124	9124	PDLIM1	PDZ and LIM domain 1 (elfin)	-1.269	2.40994463
29997	29997	GLTSCR2	Glioma tumor suppressor candidate region gene 2	-1.269	2.40994463
7447	7447	VSNL1	Visinin-like 1	-1.27	2.41161566
55118	55118	CRTAC1	Cartilage acidic protein 1	-1.274	2.41831135
7704	7704	ZBTB16	Zinc finger and BTB domain containing 16	-1.279	2.42670712
7101	7101	NR2E1	Nuclear receptor subfamily 2, group E, member 1	-1.28	2.42838977
5348	5348	FXYD1	FXYD domain containing ion transport regulator 1 (phospholemman)	-1.283	2.43344472
161291	161291	TMEM30B	Transmembrane protein 30B	-1.283	2.43344472
9231	9231	DLG5	Discs, large homolog 5 (Drosophila)	-1.294	2.45206972
54873	54873	PALMD	Palmdelphin	-1.297	2.45717396
5742	5742	PTGS1	Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	-1.3	2.46228883
9076	9076	CLDN1	Claudin 1	-1.302	2.46570465
224	224	ALDH3A2	Aldehyde dehydrogenase 3 family, member A2	-1.319	2.49493114
26751	26751	SH3YL1	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	-1.326	2.50706604
54361	54361	WNT4	Wingless-type MMTV integration site family, member 4	-1.327	2.50880441
54566	54566	EPB41L4B	Erythrocyte membrane protein band 4.1 like 4B	-1.337	2.52625452
6095	6095	RORA	RAR-related orphan receptor A	-1.341	2.53326851
259217	259217	HSPA12A	Heat shock 70kDa protein 12A	-1.345	2.54030197
10628	10628	TXNIP	Thioredoxin interacting protein	-1.347	2.54382601
54829	54829	ASPN	Asporin	-1.349	2.54735495
7850	7850	IL1R2	Interleukin 1 receptor, type II	-1.351	2.55088878
217	217	ALDH2	Aldehyde dehydrogenase 2 family (mitochondrial)	-1.354	2.55619873
10218	10218	ANGPTL7	Angiopoietin-like 7	-1.356	2.55974483
10265	10265	IRX5	Iroquois homeobox 5	-1.358	2.56329585
222	222	ALDH3B2	Aldehyde dehydrogenase 3 family, member B2	-1.363	2.57219497
23037	23037	PDZD2	PDZ domain containing 2	-1.365	2.57576326
51302	51302	CYP39A1	Cytochrome P450, family 39, subfamily A, polypeptide 1	-1.365	2.57576326
6820	6820	SULT2B1	Sulfotransferase family, cytosolic, 2B, member 1	-1.375	2.59367911
4493	4493	MT1E	Metallothionein 1E	-1.383	2.60810147
8710	8710	SERPINB7	Serpin peptidase inhibitor, clade B (ovalbumin), member 7	-1.386	2.61353051
999	999	CDH1	Cadherin 1, type 1, E-cadherin (epithelial)	-1.394	2.62806325
10848	10848	PPP1R13L	Protein phosphatase 1, regulatory (inhibitor) subunit 13 like	-1.394	2.62806325
85453	85453	TSPYL5	TSPY-like 5	-1.401	2.64084568
10418	10418	SPON1	Spondin 1, extracellular matrix protein	-1.403	2.64450921
1287	1287	COL4A5	Collagen, type IV, alpha 5 (Alport syndrome)	-1.405	2.64817782

1012	1012	CDH13	Cadherin 13, H-cadherin (heart)	-1.407	2.65185152
1675	1675	CFD	Complement factor D (adipsin)	-1.41	2.65737163
80004	80004	RBM35B	RNA binding motif protein 35B	-1.419	2.67400099
51200	51200	CPA4	Carboxypeptidase A4	-1.42	2.67585511
2861	2861	GPR37	G protein-coupled receptor 37 (endothelin receptor type B-like)	-1.421	2.67771051
10089	10089	KCNK7	Potassium channel, subfamily K, member 7	-1.421	2.67771051
3606	3606	IL18	Interleukin 18 (interferon-gamma-inducing factor)	-1.422	2.6795672
55638	55638	FLJ20366	Golgi-localized protein	-1.422	2.6795672
651872	651872	LOC651872		-1.422	2.6795672
7286	7286	TUFT1	Tuftelin 1	-1.425	2.68514501
79026	79026	AHNAK	AHNAK nucleoprotein	-1.432	2.69820507
646	646	BNC1	Basonuclin 1	-1.433	2.70007597
57447	57447	NDRG2	NDRG family member 2	-1.433	2.70007597
11187	11187	PKP3	Plakophilin 3	-1.439	2.71132865
3909	3909	LAMA3	Laminin, alpha 3	-1.44	2.71320865
83604	83604	TMEM47	Transmembrane protein 47	-1.445	2.72262823
5325	5325	PLAGL1	Pleiomorphic adenoma gene-like 1	-1.448	2.72829567
6317	6317	SERPINB3	Serpin peptidase inhibitor, clade B (ovalbumin), member 3	-1.453	2.73776763
1272	1272	CNTN1	Contactin 1	-1.454	2.73966596
9022	9022	CLIC3	Chloride intracellular channel 3	-1.461	2.7529912
55612	55612	C20orf42	Chromosome 20 open reading frame 42	-1.463	2.75681031
4948	4948	OCA2	Oculocutaneous albinism II (pink-eye dilution homolog, mouse)	-1.465	2.76063471
57152	57152	SLURP1	Secreted LY6/PLAUR domain containing 1	-1.47	2.77021894
3868	3868	KRT16	Keratin 16 (focal non-epidermolytic palmoplantar keratoderma)	-1.473	2.77598544
2628	2628	GATM	Glycine amidinotransferase (L-arginine:glycine amidinotransferase)	-1.474	2.77791027
218	218	ALDH3A1	Aldehyde dehydrogenase 3 family, memberA1	-1.476	2.78176394
2263	2263	FGFR2	Fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome)	-1.483	2.79529394
22798	22798	LAMB4	Laminin, beta 4	-1.49	2.80888975
81578	81578	COL21A1	Collagen, type XXI, alpha 1	-1.496	2.82059592
4023	4023	LPL	Lipoprotein lipase	-1.499	2.82646729
9355	9355	LHX2	LIM homeobox 2	-1.5	2.82842712
1634	1634	DCN	Decorin	-1.502	2.83235088
1382	1382	CRABP2	Cellular retinoic acid binding protein 2	-1.506	2.84021472
28231	28231	SLCO4A1	Solute carrier organic anion transporter family, member 4A1	-1.517	2.86195304
10276	10276	NET1	Neuroepithelial cell transforming gene 1	-1.52	2.8679105
3397	3397	ID1	Inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	-1.521	2.86989907
760	760	CA2	Carbonic anhydrase II	-1.528	2.88385774
6785	6785	ELOVL4	Elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 4	-1.534	2.89587634
7123	7123	CLEC3B	C-type lectin domain family 3, member B	-1.534	2.89587634
5055	5055	SERPINB2	Serpin peptidase inhibitor, clade B (ovalbumin), member 2	-1.537	2.90190442
1956	1956	EGFR	Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	-1.556	2.94037467
25797	25797	QPCT	Glutaminyl-peptide cyclotransferase (glutaminyl cyclase)	-1.557	2.94241349
7164	7164	TPD52L1	Tumor protein D52-like 1	-1.559	2.94649537
64919	64919	BCL11B	B-cell CLL/lymphoma 11B (zinc finger protein)	-1.562	2.95262881
2940	2940	GSTA3	Glutathione S-transferase A3	-1.563	2.95467613
1040	1040	CDS1	CDP-diacylglycerol synthase (phosphatidate cytidylyltransferase) 1	-1.569	2.96698987
2707	2707	GJB3	Gap junction protein, beta 3, 31kDa	-1.573	2.97522752
2051	2051	EPHB6	EPH receptor B6	-1.589	3.0084075
23641	23641	LDOC1	Leucine zipper, down-regulated in cancer 1	-1.592	3.01466982
79852	79852	ABHD9	Abhydrolase domain containing 9	-1.597	3.02513599
53905	53905	DUOX1	Dual oxidase 1	-1.603	3.03774338
92211	92211	PCDH21	Protocadherin 21	-1.604	3.03984971
3898	3898	LAD1	Ladinin 1	-1.605	3.04195751
8857	8857	FCGBP	Fc fragment of IgG binding protein	-1.605	3.04195751
80740	80740	LY6G6C	Lymphocyte antigen 6 complex, locus G6C	-1.615	3.06311599
4501	4501	MT1X	Metallothionein 1X	-1.616	3.06523992
79652	79652	C16orf30	Chromosome 16 open reading frame 30	-1.633	3.10157283
202	202	AIM1	Absent in melanoma 1	-1.635	3.1058755
8626	8626	TP73L	Tumor protein p63	-1.639	3.11449876
51765	51765	RP6-213H19.1	Serine/threonine protein kinase MST4	-1.644	3.12531152
358	358	AQP1	Aquaporin 1 (Colton blood group)	-1.648	3.13398875

6337	6337	SCNN1A	Sodium channel, nonvoltage-gated 1 alpha	-1.655	3.14923191
51195	51195	RAPGEFL1	Rap guanine nucleotide exchange factor (GEF)-like 1	-1.66	3.16016525
2173	2173	FABP7	Fatty acid binding protein 7, brain	-1.661	3.16235647
3131	3131	HLF	Hepatic leukemia factor	-1.665	3.17113655
10752	10752	CHL1	Cell adhesion molecule with homology to L1CAM (close homolog of L1)	-1.67	3.18214594
5507	5507	PPP1R3C	Protein phosphatase 1, regulatory (inhibitor) subunit 3C	-1.682	3.20872467
10974	10974	C10orf116	Chromosome 10 open reading frame 116	-1.683	3.21094955
1396	1396	CRIP1	Cysteine-rich protein 1 (intestinal)	-1.688	3.22209716
1718	1718	DHCR24	24-dehydrocholesterol reductase	-1.689	3.22433133
6698	6698	SPRR1A	Small proline-rich protein 1A	-1.712	3.27614679
2259	2259	FGF14	Fibroblast growth factor 14	-1.719	3.29208138
64131	64131	XYLT1	Xylosyltransferase I	-1.725	3.30580127
909	909	CD1A	CD1a molecule	-1.726	3.30809347
7739	7739	ZNF185	Zinc finger protein 185 (LIM domain)	-1.777	3.42712782
1041	1041	CDSN	Corneodesmosin	-1.781	3.43664302
3983	3983	ABLIM1	Actin binding LIM protein 1	-1.812	3.51128719
9314	9314	KLF4	Kruppel-like factor 4 (gut)	-1.849	3.60250392
3613	3613	IMPA2	Inositol(myo)-1(or 4)-monophosphatase 2	-1.859	3.62756132
51673	51673	CGI-38	Tubulin polymerization-promoting protein family member 3	-1.86	3.63007662
3120	3120	HLA-DQB2		-1.864	3.6401553
7277	7277	TUBA4A	Tubulin, alpha 4a	-1.864	3.6401553
10653	10653	SPINT2	Serine peptidase inhibitor, Kunitz type, 2	-1.871	3.65786036
771	771	CA12	Carbonic anhydrase XII	-1.886	3.69609029
4308	4308	TRPM1	Transient receptor potential cation channel, subfamily M, member 1	-1.896	3.72179863
25984	25984	KRT23	Keratin 23 (histone deacetylase inducible)	-1.914	3.7685251
25833	25833	POU2F3	POU class 2 homeobox 3	-1.931	3.81319418
5650	5650	KLK7	Kallikrein-related peptidase 7	-1.938	3.83174087
3815	3815	KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	-1.944	3.84770982
84909	84909	C9orf3	Chromosome 9 open reading frame 3	-1.952	3.86910532
2487	2487	FRZB	Frizzled-related protein	-1.967	3.90954307
11202	11202	KLK8	Kallikrein-related peptidase 8	-1.987	3.96411825
6382	6382	SDC1	Syndecan 1	-1.99	3.97236998
6590	6590	SLPI	Secretory leukocyte peptidase inhibitor	-2.004	4.01110574
9982	9982	FGFBP1	Fibroblast growth factor binding protein 1	-2.01	4.0278222
8424	8424	BBOX1	Butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1	-2.077	4.21928927
79983	79983	POF1B	Premature ovarian failure, 1B	-2.082	4.23393758
3713	3713	IVL	Involucrin	-2.107	4.3079455
1428	1428	CRYM	Crystallin, mu	-2.148	4.43212939
3034	3034	HAL	Histidine ammonia-lyase	-2.153	4.44751663
4118	4118	MAL	Mal, T-cell differentiation protein	-2.208	4.62034314
2205	2205	FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	-2.229	4.68808913
563	563	AZGP1	Alpha-2-glycoprotein 1, zinc-binding	-2.251	4.76012679
63928	63928	LOC63928	Calcineurin B homologous protein 2	-2.253	4.7667303
1672	1672	DEFB1	Defensin, beta 1	-2.265	4.8065442
10874	10874	NMU	Neuromedin U	-2.286	4.87702038
383	383	ARG1	Arginase, liver	-2.306	4.94510104
2878	2878	GPX3	Glutathione peroxidase 3 (plasma)	-2.323	5.00371632
3728	3728	JUP	Junction plakoglobin	-2.323	5.00371632
25818	25818	KLK5	Kallikrein-related peptidase 5	-2.327	5.01760882
2625	2625	GATA3	GATA binding protein 3	-2.336	5.04900813
25891	25891	DKFZP586H2123	Regeneration associated muscle protease	-2.351	5.10177757
2261	2261	FGFR3	Fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	-2.386	5.22706102
11012	11012	KLK11	Kallikrein-related peptidase 11	-2.393	5.2524845
57111	57111	RAB25	RAB25, member RAS oncogene family	-2.398	5.27071981
2697	2697	GJA1	Gap junction protein, alpha 1, 43kDa	-2.422	5.35913441
810	810	CALML3	Calmodulin-like 3	-2.507	5.68436817
3854	3854	KRT6B		-2.553	5.86853338
10850	10850	CCL27	Chemokine (C-C motif) ligand 27	-2.637	6.22036829
1308	1308	COL17A1	Collagen, type XVII, alpha 1	-2.719	6.58416276
445	445	ASS1	Argininosuccinate synthetase 1	-2.724	6.60702132
3872	3872	KRT17	Keratin 17	-2.745	6.70389708
79755	79755	ZNF750	Zinc finger protein 750	-2.748	6.71785194
1525	1525	CXADR	Coxsackie virus and adenovirus receptor	-2.766	6.80219328

688	688	KLF5	Kruppel-like factor 5 (intestinal)	-2.814	7.03231649
7306	7306	TYRP1	Tyrosinase-related protein 1	-2.815	7.03719261
5764	5764	PTN	Pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	-2.846	7.19004101
1830	1830	DSG3	Desmoglein 3 (pemphigus vulgaris antigen)	-2.867	7.29546532
3853	3853	KRT6A	Keratin 6A	-2.878	7.35130307
27076	27076	LYPD3	LY6/PLAUR domain containing 3	-2.925	7.59473697
9890	9890	LPPR4	Plasticity related gene 1	-2.974	7.85711676
360	360	AQP3	Aquaporin 3 (Gill blood group)	-3.022	8.12292881
57402	57402	S100A14	S100 calcium binding protein A14	-3.029	8.16243727
9635	9635	CLCA2	Chloride channel, calcium activated, family member 2	-3.035	8.19645458
8796	8796	SCEL	Sciellin	-3.048	8.27064589
3075	3075	CFH	Complement factor H	-3.057	8.32240213
3858	3858	KRT10	Keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	-3.086	8.49138567
26239	26239	LCE2B	Late cornified envelope 2B	-3.094	8.5386027
23650	23650	TRIM29	Tripartite motif-containing 29	-3.133	8.77257271
4070	4070	TACSTD2	Tumor-associated calcium signal transducer 2	-3.172	9.01295383
6279	6279	S100A8	S100 calcium binding protein A8	-3.204	9.21510114
7021	7021	TFAP2B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	-3.225	9.35021799
64065	64065	PERP	PERP, TP53 apoptosis effector	-3.274	9.67324541
5493	5493	PPL	Periplakin	-3.28	9.71355908
23086	23086	EXPH5	Exophilin 5	-3.299	9.84233076
6699	6699	SPRR1B	Small proline-rich protein 1B (cornifin)	-3.314	9.94519735
113146	113146	C14orf78	AHNAK nucleoprotein 2	-3.332	10.0700574
667	667	DST	Dystonin	-3.339	10.1190363
51806	51806	CALML5	Calmodulin-like 5	-3.449	10.9207497
2810	2810	SFN	Stratifin	-3.479	11.1502179
6273	6273	S100A2	S100 calcium binding protein A2	-3.555	11.7533491
84525	84525	HOP	HOP homeobox	-3.679	12.808237
11005	11005	SPINK5	Serine peptidase inhibitor, Kazal type 5	-3.68	12.817118
1474	1474	CST6	Cystatin E/M	-3.774	13.6800348
1475	1475	CSTA	Cystatin A (stefin A)	-3.843	14.3502106
8581	8581	LY6D	Lymphocyte antigen 6 complex, locus D	-3.905	14.980356
1825	1825	DSC3	Desmocollin 3	-4.051	16.5757242
3849	3849	KRT2	Keratin 2 (epidermal ichthyosis bullosa of Siemens)	-4.171	18.0134174
1828	1828	DSG1	Desmoglein 1	-4.196	18.3282864
4014	4014	LOR	Loricrin	-4.252	19.0537096
1832	1832	DSP	Desmoplakin	-4.607	24.3694198
1823	1823	DSC1	Desmocollin 1	-4.736	26.6488247
9547	9547	CXCL14	Chemokine (C-X-C motif) ligand 14	-4.86	29.040613
3866	3866	KRT15	Keratin 15	-4.963	31.1897482
5268	5268	SERPINB5	Serpin peptidase inhibitor, clade B (ovalbumin), member 5	-5.042	32.9452827
3852	3852	KRT5	Keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types)	-5.812	56.180595
3848	3848	KRT1	Keratin 1 (epidermolytic hyperkeratosis)	-6.635	99.388016
3861	3861	KRT14	Keratin 14 (epidermolysis bullosa simplex, Dowling-Meara, Koebner)	-7.142	141.239519

Supplemental Table 1: Significantly regulated genes in PM compared to MN, MM compared to PM, MM compared to MN with a minimum fold change of <-2 and >2.

Category	p-value	Molecules
Cancer	3,82E-27-1,08E-03	SELL, KRT6A, ASS1, KLK6, CCNB2, EIF4A2, SERPINA3, CXCL10, GPR37, CXCL13, CDKN3, FABP7, TYMS, TDO2, CKS2, GSTM3 (includes EG:2947), MT1X, IGH@, RRM2, IER3, RAB31, ARHGDIB, NRCAM, CTSB, TFRC, TCN1, PDGFD, ECM1, UBE2C, KIF20A, PRAME (includes EG:23532), FN1, GBP1 (includes EG:2633), PHLDA2, PPP1R3C, KPNA2, PTN, GDF15, CCL5, CD74, COL4A2, ABCA5, CCL2, STK17A, MAL, HLA-DRA, IGF1R, DAB2, SERPINA1, ADAMDEC1, TRIM29, MMP1 (includes EG:4312), PLAT, HEY1, PLA2G16, S100A1, PKM2, PSMB9, CCNB1, TNC, GZMK, KRT6B, KRT17, TYROBP, DST, ISG15, ITGB2, SERPINB4, S100A9, KRT5, CIRBP, SORBS2, GATA3, SGK3, GZMB, DLGAP5, RGS1, MMP3, TRIM9, PTTG1, RNASE1, MELK, LYZ, CD163, PBK, BIRC5, FGFR3, NNMT, GPX3, CCL27, CXCL14, IFI30, SCRG1, KRT1, CDKN1C, GZMA, KRT16, IL8, SPP1, CXCL9, COL4A1, GGH, SERPINB3, CAPG, AURKA, TUSC3, BST2, EFS, SPARCL1, ABCA8, AKR1B10, CD14, IRF8, CCL19, DSC1, TRA@, LGR4, CDK2, IFI27, FRZB, LETMD1, CD2, KIAA0101, TFAP2B, ACOT7, GLRX, TNFRSF12A, HLF (includes EG:3131), SOX9, KCNMA1, MCAM, F5, S100A8, CFH, STAT1, SILV, KRT14, COTL1, CXCR4, C9ORF3, PRC1, UPP1, CD36, CD48, PFKP, HCLS1, CD3D, MST4, WARS, IGJ, LGALS3BP, KLF5, ISG20, MMP9
Dermatological Diseases and Conditions	4,48E-14-1,2E-03	RGS1, SELL, KRT6A, MMP3, HLA-DRB1, KLK6, BIRC5, CCL27, CXCL13, IFI30, KRT1, DSP, TYMS, IL8, KRT16, SPP1, COL4A1, CXCL9, SERPINB3, DSG1, UBD, COL21A1, TCN1, CD14, DSC1, ECM1, LCP2, CDK2, FN1, CD2, GDF15, CCL5, CD74, COL4A2, HLA-DRA, KRT2, S100A8, SERPINA1, LOR, STAT1, MMP1 (includes EG:4312), IL11RA, PLAT, KRT14, KRT6B, CXCR4, KRT17, CD36, COL17A1, TYRP1, ITGB2, S100A9, KRT5, FCER1G, MMP9
Cellular Growth and Proliferation	1,32E-13-1,19E-03	KLK6, HLA-DRB1, CXCL10, LGMN, CDKN3, FABP7, ZBTB16, TNFRSF21, TYMS, CKS2, IL12RB2, IER3, LDOC1, NRCAM, CTSB, TFRC, BCL2A1, PDGFD, ECM1, LCP2, UBE2C, KIF20A, PRAME (includes EG:23532), FN1, GBP1 (includes EG:2633), PHLDA2, GDF15, PTN, COL4A2, CCL5, CD74, TAP1, GLTSCR2, CCL2, IGF1R, DAB2, KRT2, SERPINA1, IL11RA, HEY1, PLAT, S100A1, PKM2, PLAGL1, CCNB1, TNC, KRT17, TYROBP, ISG15, ITGB2, SWAP70, S100A9, CIRBP, FCER1G, GATA3, ID4, GZMB, SGK3, DLGAP5, MMP3, PTTG1, CD163, PBK, BIRC5, FGFR3, GPX3, CCL27, IFI30, CDKN1C, DSP, KRT16, IL8, CXCL9, COL4A1, SPP1, FXYD1, CITED1, AURKA, BST2, TPX2, EFS, CD14, IRF8, CCL19, CST6, CDK2, TRA@, LGR4, FRZB, CD2, KIAA0101, TFAP2B, TNFRSF12A, SOX9, MCAM, S100A8, STAT1, ACTN1, DTL, CXCR4, UPP1, CD36, CD48, HCLS1, CADM1, MST4, TYRP1, WARS, NR2E1 (includes EG:7101), SATB1, KLF5, A2M, MMP9, ISG20
Gastrointestinal Disease	6,92E-13-3,41E-04	DLGAP5, MMP3, TRIM9, PTTG1, CCNB2, KLK6, SERPINA3, MELK, EIF4A2, LYZ, PBK, BIRC5, NNMT, FGFR3, CXCL10, CDKN3, TYMS, IL8, SPP1, COL4A1, TDO2, MT1X, GGH, RRM2, CAPG, AURKA, BST2, RAB31, EFS, CTSB, TCN1, CD14, TFRC, LGR4, UBE2C, KIF20A, FN1, KIAA0101, KPNA2, GDF15, ABCA5, CD74, COL4A2, ACOT7, GLRX, CCL2, MCAM, HLA-DRA, IGF1R, STAT1, PLAT, PKM2, KRT14, TNC, TYROBP, CXCR4, CD36, HCLS1, WARS, CIRBP, MMP9, ISG20
Cellular Movement	1,17E-12-1,2E-03	RGS1, SELL, KRT6A, MMP3, PTTG1, KLK6, CCNB2, SERPINA3, PBK, CXCL10, LGMN, CCL27, CXCL13, CXCL14, FABP7, ZBTB16, TNFRSF21, KRT16, IL8, CXCL9, SPP1, COL4A1, SERPINB3, AURKA, ARHGDIB, EFS, NRCAM, CTSB, CD14, CCL19, PDGFD, CST6, CCL18, LGR4, LCP2, C2, FN1, GBP1 (includes EG:2633), ARPC1B, CD2, GDF15, PTN, CD74, CCL5, COL4A2, TNFRSF12A, CCL2, MCAM, IGF1R, DAB2, PTPRZ1, S100A8, SERPINA1, CFH, STAT1, CHL1, MMP1 (includes EG:4312), PLAT, CXCL11, HEY1, CD53, S100A1, TNC, CXCR4, COL17A1, CD48, CD36, CADM1, ITGB2, NR2E1 (includes EG:7101), WARS, SWAP70, S100A9, KLF5, FCER1G, GATA3, A2M, MMP9, GZMB
Inflammatory Response	1,24E-12-1,2E-03	RGS1, SELL, MMP3, ASS1, PTTG1, HLA-DRB1, C1QA, HLA-DMB, SERPINA3, C1QB, LYZ, CD163, CXCL10, CCL27, CXCL13, CXCL14, IFI30, GZMA, TNFRSF21, IL8, SPP1, CXCL9, IL12RB2, CAPG, IER3, ARHGDIB, CTSB, CD14, IRF8, CCL19, CCL18, DSC1, TRA@, LCP2, C2, FN1, CD2, CD74, CCL5, TAP1, TNFRSF12A, CCL2, F5, HLA-DRA, IGF1R, IFI6, S100A8, SERPINA1, CFH, STAT1, CXCL11, IL11RA, PLAT, SILV, PSMB9, HLA-DMA, TNC, TYROBP, CXCR4, CD48, CD36, COL17A1, ISG15, TYRP1, ITGB2, S100A9, SATB1, PI3, FCER1G, GATA3, A2M, MMP9, GZMB
Cell-To-Cell Signaling and Interaction	1,87E-12-1,2E-03	RGS1, SELL, LHX2, HLA-DRB1, KLK6, HLA-DMB, C1QA, LYZ, CD163, CXCL10, FGFR3, CXCL13, CCL27, ALDH3A2, CXCL14, LPL, FABP7, CDKN1C, KRT1, GZMA, KRT16, IL8, CXCL9, SPP1, SERPINB3, IL12RB2, BST2, ARHGDIB, ANGPTL7, NRCAM, TFRC, CD14, IRF8, CCL19, BCL2A1, CST6, CCL18, LGR4, TRA@, LCP2, CDK2, UBE2C, FN1, CD2, GDF15, CCL5, CD74, TNFRSF12A, SOX9, CCL2, KCNMA1, MCAM, HLA-DRA, F5, IGF1R, KRT2, DAB2, PTPRZ1, S100A8, CFH, STAT1, CHL1, GATM, MMP1 (includes EG:4312), PLAT, DSC3, CXCL11, PSMB9, HLA-DMA, TNC, FEZ1, TYROBP, CXCR4, FGF14, COL17A1, CD48, CD36, AZGP1, CADM1, SYBU, ITGB2, SWAP70, S100A9, LGALS3BP, SATB1, PI3, FCER1G, GATA3, A2M, MMP9, GZMB
Genetic Disorder	2,58E-12-7,09E-04	SELL, KRT6A, AUTS2 (includes EG:26053), ASS1, LRRC1, TLE1, CCNB2, EIF4A2, SERPINA3, CRYM, TYMS, RRM2, IL12RB2, DSG1, ARHGDIB, C14ORF132, CTSB, TFRC, ECM1, UBE2C, CYP39A1, GBP1 (includes EG:2633), GDF15, CCL5, CD74, CCL2, KRT2, DAB2, SERPINA1, TRIM29, CHL1, MMP1 (includes EG:4312), S100A1, PKM2, MLLT11, KRT17, DST, COL17A1, PAMR1, CSTB, ISG15, PDZD2, SWAP70, KRT5, WIPI1, DERL1, GATA3, ID4, GZMB, DLGAP5, MMP3, LHX2, PTTG1, RNASE1, LYZ, CD163, GPX3, CXCL14, LPL, CDKN1C, NEDD4L, IL8, FXYD1, CAPG, AURKA, TUSC3, TMEM204, SPARCL1, ABCA8, AKR1B10, IRF8, C2, LGR4, LETMD1, FRZB, KIAA0101, TFAP2B, GLRX, MCAM, CFH, STAT1, KRT14, SLC20A1, HLA-DMA, FEZ1, PRC1, CD36, PYGL, HSPA12A, CADM1, TYRP1, KLF5, A2M, ISG20, KLK6, HLA-DRB1, HLA-DMB, EXPH5, CXCL10, LGMN, GPR37, CDKN3, FABP7, ZBTB16, DFNA5, CKS2, TDO2, CHN1 (includes EG:1123), MT1X, IER3, RAB31, UBD, NRCAM, MS4A4A, TCN1, TRPM1, PDGFD, LCP2, FN1, TSPAN7, KPNA2, PTN, COL4A2, ABCA5, CORO2B, HLA-DRA, MAL, IGF1R, SNX10, IFI6, ADAMDEC1, LAMB4,

		RPL13, DSC3, PLAT, IL11RA, CD53, PSMB9, PLAGL1, CCNB1, TNC, CNTN1, KRT6B, OAS2, TYROBP, FGF14, CRTAC1, ITGB2, S100A9, CIRBP, FCER1G, SORBS2, TRIM9, LPPR4, MELK, PBK, BIRC5, FGFR3, CCL27, ALDH3A2, IFI30, SCEL, KRT1, DSP, GZMA, KRT16, COL4A1, SPP1, CXCL9, XYLT1, PHACTR1, GGH, SERPINB3, TMEM47, BST2, COL21A1, CD14, DSC1, CCL18, CDK2, TRA@, CD2, CDHR1, APOC2, ACOT7, TNFRSF12A, SOX9, KCNMA1, F5, PTPRZ1, S100A8, LOR, GATM, ACTN1, FAM149A, COTL1, CXCR4, C9ORF3, CD48, AHCYL2, PFKP, CD3D, KCNJ13, SYBU, NR2E1 (includes EG:7101), IGJ, MMP9
Hematological System Development and Function	1,14E-11-1,2E-03	RGS1, SELL, MMP3, CCNB2, HLA-DRB1, HLA-DMB, C1QA, SERPINA3, LYZ, CD163, BIRC5, CXCL10, CCL27, CXCL13, CXCL14, ZBTB16, GZMA, TNFRSF21, IL8, COL4A1, SPP1, CXCL9, IL12RB2, IER3, EFS, CTSB, CD14, CCL19, IRF8, DSC1, CCL18, BCL2A1, C2, CDK2, LCP2, TRA@, FN1, CD2, CD74, CCL5, TAP1, CCL2, HLA-DRA, F5, IGF1R, DAB2, S100A8, SERPINA1, CFH, STAT1, MMP1 (includes EG:4312), CXCL11, PLAT, IL11RA, PSMB9, HLA-DMA, TNC, CCNB1, CXCR4, TYROBP, COL17A1, CD36, CD48, HCLS1, CD3D, ISG15, CADM1, TYRP1, ITGB2, SWAP70, S100A9, PI3, SATB1, FCER1G, GATA3, A2M, MMP9, ISG20, GZMB
Immune Cell Trafficking	1,14E-11-1,2E-03	RGS1, SELL, MMP3, HLA-DRB1, SERPINA3, C1QA, HLA-DMB, LYZ, CD163, CXCL10, CXCL13, CCL27, CXCL14, ZBTB16, GZMA, TNFRSF21, IL8, COL4A1, SPP1, CXCL9, SERPINB3, IER3, EFS, CTSB, CD14, CCL19, CCL18, DSC1, LCP2, C2, FN1, CD2, CCL5, CD74, CCL2, HLA-DRA, F5, SERPINA1, S100A8, CFH, STAT1, CXCL11, PLAT, HLA-DMA, PSMB9, TNC, TYROBP, CXCR4, CD48, COL17A1, CD36, ITGB2, SWAP70, S100A9, SATB1, FCER1G, GATA3, MMP9, GZMB
Tissue Morphology	5,1E-11-1,2E-03	SELL, MMP3, PTTG1, C1QA, BIRC5, FGFR3, CXCL10, CXCL13, CDKN1C, ZBTB16, TYMS, TNFRSF21, IL8, SPP1, COL4A1, IL12RB2, CTSB, IRF8, CCL19, BCL2A1, TRA@, LCP2, CDK2, FN1, GDF15, COL4A2, CCL5, TAP1, SOX9, CCL2, IGF1R, SERPINA1, S100A8, CFH, STAT1, MMP1 (includes EG:4312), PLAT, S100A1, TNC, CCNB1, CXCR4, TYROBP, PRC1, CD3D, ISG15, CADM1, ITGB2, NR2E1 (includes EG:7101), SWAP70, S100A9, IGJ, PI3, SATB1, FCER1G, GATA3, MMP9
Cellular Development	3,77E-10-1,2E-03	SELL, KRT6A, LPXN, SSBP2, SERPINA3, CXCL10, FABP7, ZBTB16, TYMS, DFNA5, CHN1 (includes EG:1123), IL12RB2, IER3, CTSB, TRPM1, TFRC, BCL2A1, LCP2, PRAME (includes EG:23532), FN1, TSPAN7, PTN, GDF15, CD74, CCL5, SPRR1A, CCL2, MAL, IGF1R, DAB2, CHL1, MMP1 (includes EG:4312), HEY1, PLAT, IL11RA, S100A1, PSMB9, PLAGL1, IVL, CCNB1, TNC, TYROBP, ITGB2, S100A9, FCER1G, GATA3, CHRDL1, ID4, GZMB, DLGAP5, MMP3, LHX2, RNASE1, CD163, BIRC5, FGFR3, SCEL, CDKN1C, DSP, GZMA, IL8, SPP1, COL4A1, CAPG, CITED1, CD14, IRF8, CCL19, DSC1, TRA@, CDK2, CD2, FRZB, TFAP2B, TNFRSF12A, SOX9, KCNMA1, F5, PTPRZ1, S100A8, STAT1, LOR, CXCL11, HLA-DMA, CXCR4, FEZ1, SPRR1B, CD36, CD3D, HCLS1, CADM1, MST4, TYRP1, NR2E1 (includes EG:7101), SATB1, KLF5, A2M, MMP9
Reproductive System Disease	1,25E-09-5,64E-04	SELL, KRT6A, ASS1, KLK6, CXCL10, LGMN, CXCL13, FABP7, ZBTB16, TYMS, MT1X, GSTM3 (includes EG:2947), RRM2, IER3, ARHGDIB, CTSB, TCN1, TFRC, PDGFD, ECM1, UBE2C, PRAME (includes EG:23532), KIF20A, FN1, PHLDA2, KPNA2, GDF15, CD74, ABCA5, CCL5, CCL2, IGF1R, DAB2, SERPINA1, ADAMDEC1, MMP1 (includes EG:4312), S100A1, PSMB9, CCNB1, TNC, CNTN1, KRT6B, KRT17, DST, ISG15, SERPINB4, S100A9, CIRBP, KRT5, SORBS2, GATA3, SGK3, RGS1, MMP3, TRIM9, PTTG1, LYZ, CD163, PBK, BIRC5, FGFR3, GPX3, CXCL14, IFI30, SCRG1, KRT1, CDKN1C, GZMA, IL8, CXCL9, SPP1, COL4A1, SERPINB3, AURKA, TUSC3, ABCA8, CD14, CCL19, CCL18, LGR4, CDK2, LETMD1, IFI27, KIAA0101, SOX9, KCNMA1, MCAM, S100A8, CFH, STAT1, CXCR4, C9ORF3, PRC1, UPP1, CADM1, IGJ, MMP9, ISG20
Hair and Skin Development and Function	1,39E-09-4,66E-04	KRT14, KRT16, IVL, FN1, SPRR1B, KRT17, COL17A1, CITED1, SPRR1A, TYRP1, KRT5, ALDH3A2, TRPM1, KRT2, SCEL, LOR, CST6, KRT1, KRT15, DSP
Organ Development	1,39E-09-1,39E-09	KRT14, KRT16, SPRR1B, KRT17, COL17A1, SPRR1A, KRT5, ALDH3A2, KRT2, SCEL, CST6, KRT1, KRT15, DSP
Immunological Disease	4,2E-09-1,2E-03	SELL, MMP3, TRIM9, AUTS2 (includes EG:26053), LRRC1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, LYZ, BIRC5, FGFR3, CXCL10, CXCL13, CXCL14, IFI30, NEDD4L, TYMS, TNFRSF21, GZMA, IL8, SPP1, COL4A1, CXCL9, XYLT1, RRM2, IL12RB2, TUSC3, TPX2, DSG1, RAB31, ARHGDIB, NRCAM, CTSB, CD14, TFRC, IRF8, CCL19, CCL18, DSC1, CDK2, LCP2, C2, FN1, CD2, FRZB, CCL5, COL4A2, CD74, ACOT7, TAP1, HLA-DPA1, TNFRSF12A, CCL2, KCNMA1, HLA-DRA, IGF1R, S100A8, CFH, STAT1, CHL1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, S100A1, CD53, PSMB9, HLA-DMA, CCNB1, TYROBP, CXCR4, C9ORF3, FGF14, COL17A1, CD36, HCLS1, CD3D, CADM1, PDZD2, ITGB2, WARS, SWAP70, S100A9, FCER1G, SORBS2, GATA3, A2M, MMP9, GZMB
Cell-mediated Immune Response	5,9E-09-6,23E-04	SELL, FN1, CD2, CCNB2, CD74, CCL5, BIRC5, CXCL10, CXCL13, CCL27, CCL2, F5, IGF1R, STAT1, CXCL11, GZMA, TNFRSF21, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, COL4A1, CXCL9, CXCR4, CD48, SERPINB3, IL12RB2, IER3, CD3D, EFS, ITGB2, SATB1, FCER1G, IRF8, CCL19, GATA3, CCL18, BCL2A1, LCP2, TRA@, CDK2, GZMB
Cell Death	8,25E-09-1,2E-03	HSPB2, HLA-DRB1, SERPINA3, C1QA, CXCL10, GPR37, ZBTB16, TYMS, TNFRSF21, MT1X, RRM2, IL12RB2, IER3, DSG1, UBD, NRCAM, CTSB, TFRC, BCL2A1, UBE2C, PRAME (includes EG:23532), FN1, PHLDA2, GDF15, PTN, CCL5, COL4A2, CD74, SPRR1A, TAP1, CCL2, STK17A, MAL, IGF1R, DAB2, IFI6, SERPINA1, CHL1, MMP1 (includes EG:4312), IL11RA, HEY1, PLAT, PLA2G16, PKM2, CD53, S100A1, PLAGL1, GZMK, TNC, CCNB1, TYROBP, SERPINB4, ITGB2, SWAP70, S100A9, FCER1G, SORBS2, ID4, GZMB, SGK3, MMP3, PTTG1, RNASE1, LYZ, PBK, BIRC5, FGFR3, CCL27, CDKN1C, DSP, GZMA, IL8, CXCL9, SPP1, SERPINB3, AURKA, CD14, IRF8, CCL19, CDK2, TRA@, FRZB, CD2, TFAP2B, CDHR1, GLRX, TNFRSF12A, HLF (includes EG:3131), SOX9, KCNMA1, MCAM, PTPRZ1, S100A8, CFH, STAT1, CXCL11, HLA-DMA, CXCR4, CD36, CD48, HCLS1, CADM1,

		MST4, NR2E1 (includes EG:7101), LGALS3BP, KLF5, SATB1, A2M, MMP9
Tissue Development	1,32E-08-1,2E-03	RGS1, SELL, MMP3, PTTG1, KLK6, C1QA, BIRC5, FGFR3, CXCL10, CDKN1C, TNFRSF21, IL8, KRT16, COL4A1, CXCL9, SPP1, IER3, AURKA, CITED1, TPX2, ARHGDIB, NRCAM, CCL19, DSC1, CST6, LCP2, FN1, CD2, PTN, COL4A2, CCL5, TNFRSF12A, SOX9, CCL2, MCAM, IGF1R, DAB2, PTPRZ1, S100A8, STAT1, CHL1, MMP1 (includes EG:4312), IL11RA, PLAT, DSC3, CXCL11, TNC, FEZ1, CXCR4, CD36, CD48, AZGP1, HCLS1, CADM1, ITGB2, SWAP70, S100A9, LGALS3BP, KLF5, FCER1G, MMP9, GZMB
Inflammatory Disease	2,62E-07-1,2E-03	SELL, AUTS2 (includes EG:26053), LRRC1, TLE1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, CXCL10, CXCL13, TYMS, TNFRSF21, TDO2, RRM2, IL12RB2, ARHGDIB, RAB31, CTSB, TFRC, BCL2A1, LCP2, FN1, CCL5, COL4A2, CD74, TAP1, HLA-DPA1, CCL2, HLA-DRA, IGF1R, KRT2, IFI6, SERPINA1, MMP1 (includes EG:4312), RPL13, LAMB4, IL11RA, PLAT, CD53, PSMB9, CCNB1, TNC, OAS2, TYROBP, DST, FGF14, ITGB2, PDZD2, SWAP70, S100A9, FCER1G, SORBS2, GATA3, GZMB, MMP3, LHX2, TRIM9, LYZ, CD163, BIRC5, FGFR3, CXCL14, IFI30, NEDD4L, GZMA, IL8, SPP1, CXCL9, COL4A1, XYLT1, TMEM47, CD14, CCL19, DSC1, CCL18, C2, TRA@, LGR4, CDK2, CD2, FRZB, CDHR1, ACOT7, TNFRSF12A, KCNMA1, F5, PTPRZ1, S100A8, CFH, STAT1, HLA-DMA, CXCR4, COTL1, C9ORF3, CD48, CD36, AZGP1, CD3D, HCLS1, CADM1, A2M, MMP9
Infection Mechanism	3,8E-07-5,09E-04	IL8, CXCL9, FN1, CXCR4, CD74, CCL5, BST2, CXCL10, ITGB2, S100A9, CCL2, PI3, SNX10, S100A8, SERPINA1, IRF8, CXCL11
Infectious Disease	3,8E-07-8,81E-04	TRIM9, PTTG1, C1QA, LYZ, CD163, CXCL10, LPL, IFI30, NEDD4L, TYMS, IL8, SPP1, CXCL9, MT1X, RRM2, IL12RB2, IER3, RAB31, UBD, MS4A4A, CTSB, TFRC, TCN1, CD14, IRF8, C2, LCP2, UBE2C, FN1, LAPTM5, GDF15, CD74, CCL5, GLTSCR2, CCL2, F5, IGF1R, PTPRZ1, SERPINA1, TRIM29, STAT1, ACTN1, CXCL11, PLAT, SLC20A1, S100A1, CXCR4, CD36, PYGL, ITGB2, S100A9, PI3, FCER1G, GATA3, A2M, MMP9
Respiratory Disease	5,8E-07-7,09E-04	PTTG1, KLK6, CCNB2, HLA-DRB1, RNASE1, LYZ, BIRC5, FGFR3, CXCL10, IFI30, CDKN1C, TYMS, IL8, SPP1, CKS2, SERPINB3, RRM2, AURKA, IER3, RAB31, AKR1B10, TCN1, CD14, CCL19, IRF8, UBE2C, FN1, CCL5, SOX9, CCL2, KCNMA1, HLA-DRA, F5, IGF1R, SERPINA1, STAT1, ACTN1, CXCL11, PLAT, IVL, TNC, CCNB1, KRT6B, CXCR4, PYGL, PFKP, AZGP1, ITGB2, S100A9, KRT5, IGJ, GATA3, MMP9, GZMB
Neurological Disease	6,54E-07-6,6E-04	SELL, KRT6A, AUTS2 (includes EG:26053), HLA-DRB1, TLE1, EIF4A2, C1QA, HLA-DMB, SERPINA3, CXCL10, GPR37, CRYM, FABP7, ZBTB16, TYMS, TNFRSF21, DFNA5, CHN1 (includes EG:1123), MT1X, RRM2, IL12RB2, IER3, ARHGDIB, RAB31, C14ORF132, NRCAM, MS4A4A, CTSB, TCN1, TRPM1, PDGFD, ECM1, UBE2C, TSPAN7, GBP1 (includes EG:2633), PTN, COL4A2, CD74, CCL5, CORO2B, CCL2, HLA-DRA, MAL, SNX10, IGF1R, SERPINA1, CHL1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, DSC3, S100A1, PKM2, PSMB9, MLLT11, CCNB1, TNC, CNTN1, TYROBP, KRT17, DST, FGF14, CSTB, PAMR1, ITGB2, PDZD2, SWAP70, S100A9, CIRBP, WIPI1, FCER1G, SORBS2, GATA3, ID4, GZMB, DLGAP5, PTTG1, LPPR4, FGFR3, CCL27, LPL, SCEL, CDKN1C, DSP, KRT16, IL8, SPP1, COL4A1, PHACTR1, FXYD1, TMEM47, CAPG, TUSC3, TMEM204, SPARCL1, CD14, IRF8, DSC1, TRA@, CDK2, LETMD1, APOC2, ACOT7, GLRX, TNFRSF12A, SOX9, KCNMA1, F5, STAT1, GATM, FAM149A, KRT14, HLA-DMA, FEZ1, CXCR4, CD36, PYGL, PFKP, HSPA12A, KLF5, A2M, MMP9
Cell Signaling	9,66E-07-1,55E-04	RGS1, SELL, FN1, CD2, PTN, APOC2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, IGF1R, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, CNTN1, SPP1, CXCL9, TYROBP, CXCR4, CD36, CD48, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2
Molecular Transport	9,66E-07-1,08E-04	RGS1, SELL, FN1, CD2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, SPP1, CXCL9, TYROBP, CXCR4, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2
Vitamin and Mineral Metabolism	9,66E-07-1,08E-04	RGS1, SELL, FN1, CD2, CCL5, LYZ, CXCL10, CCL27, CXCL13, CCL2, MCAM, S100A8, MMP1 (includes EG:4312), CXCL11, S100A1, IL8, SPP1, CXCL9, TYROBP, CXCR4, FXYD1, CD3D, ITGB2, S100A9, FCER1G, CCL19, A2M, TRA@, LCP2
Tumor Morphology	1,04E-06-1,19E-03	CD53, FN1, MMP3, CXCR4, MCAM, GDF15, CD14, ZBTB16, MMP1 (includes EG:4312), MMP9, GZMB
Cardiovascular System Development and Function	1,33E-06-1,2E-03	SELL, FN1, GBP1 (includes EG:2633), MMP3, PTN, C1QA, CCL5, COL4A2, TNFRSF12A, FGFR3, CXCL10, CCL2, F5, CXCL14, MMP1 (includes EG:4312), HEY1, CXCL11, PLAT, S100A1, IL8, SPP1, COL4A1, CXCL9, CXCR4, CD36, CITED1, ITGB2, WARS, NR2E1 (includes EG:7101), KLF5, CTSB, ECM1, MMP9
Cell Morphology	1,91E-06-1,19E-03	SELL, FN1, KRT6A, TSPAN7, LPXN, SERPINA3, CCL5, CD74, CXCL10, CCL2, KRT2, DAB2, IL8, SPP1, TNC, CXCL9, KRT17, CHN1 (includes EG:1123), IL12RB2, CAPG, ITGB2, SWAP70, CCL19, GATA3, A2M, MMP9, GZMB
Antigen Presentation	1,95E-06-1,2E-03	RGS1, SELL, FN1, HLA-DRB1, HLA-DMB, CCL5, CD74, CXCL10, CCL2, CXCL13, CXCL14, HLA-DRA, IFI30, S100A8, SERPINA1, CFH, STAT1, CXCL11, PSMB9, IL8, HLA-DMA, CXCL9, SPP1, CXCR4, TYROBP, CD36, IL12RB2, ITGB2, S100A9, PI3, FCER1G, CD14, IRF8, CCL19, CCL18, MMP9
Cellular Function and Maintenance	2,12E-06-1,19E-03	FN1, CD2, CCNB2, CCL5, CD74, BIRC5, CCL2, CXCL13, F5, IGF1R, STAT1, IL11RA, GZMA, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, CXCR4, TYROBP, IL12RB2, IER3, CD3D, ITGB2, SATB1, FCER1G, CCL19, IRF8, GATA3, BCL2A1, LCP2, TRA@, CDK2, GZMB
Lymphoid Tissue Structure and Development	3,08E-06-1,19E-03	IL8, SELL, CXCL9, SPP1, MMP3, C1QA, CCL5, BIRC5, CXCL10, ITGB2, CCL2, CXCL13, S100A9, CXCL14, PI3, FCER1G, S100A8, SERPINA1, IRF8, CFH, ZBTB16, MMP9
Hematopoiesis	5,05E-06-1,2E-03	SELL, FN1, CD2, CCL5, CD74, BIRC5, CXCL10, CCL2, F5, IGF1R, SERPINA1, S100A8, STAT1, ZBTB16, IL11RA, CXCL11, GZMA, HLA-DMA, PSMB9, IL8, SPP1, CCNB1, CXCL9, CXCR4, IL12RB2, IER3, CD3D, ITGB2, S100A9, SATB1, FCER1G, CD14, IRF8, CCL19, GATA3, BCL2A1, TRA@, LCP2, CDK2, MMP9, GZMB

Humoral Immune Response	6,32E-06-1,2E-03	RGS1, EFS, CXCL9, CXCL13, CCL19, CCL18, MMP9
Cellular Compromise	6,36E-06-6,36E-04	IL8, FN1, KRT6A, SPP1, TYROBP, TYRP1, ITGB2, CCL2, PI3, FCER1G, CD14, IRF8, CFH
Connective Tissue Disorders	6,46E-06-1,82E-04	MMP3, AUTS2 (includes EG:26053), TRIM9, LRRC1, HLA-DRB1, HLA-DMB, SERPINA3, C1QA, LYZ, BIRC5, FGFR3, CXCL10, CXCL13, CXCL14, TNFRSF21, GZMA, IL8, COL4A1, SPP1, CXCL9, XYLT1, ARHGDIB, RAB31, COL21A1, CTSB, TFRC, CCL19, DSC1, CCL18, CDK2, TRA@, C2, FN1, FRZB, CCL5, COL4A2, CD74, ACOT7, TAP1, HLA-DPA1, CCL2, KCNMA1, HLA-DRA, S100A8, STAT1, MMP1 (includes EG:4312), RPL13, LAMB4, PLAT, IL11RA, CD53, HLA-DMA, PSMB9, CCNB1, CXCR4, C9ORF3, FGF14, COL17A1, CD36, AZGP1, HCLS1, CD3D, CADM1, PDZD2, ITGB2, SWAP70, S100A9, FCER1G, SORBS2, A2M, MMP9, GZMB
Skeletal and Muscular Disorders	6,46E-06-1,82E-04	AUTS2 (includes EG:26053), ASS1, LRRC1, HLA-DRB1, C1QA, SERPINA3, HLA-DMB, EIF4A2, CXCL10, CXCL13, CRYM, FABP7, ZBTB16, TNFRSF21, TYMS, CKS2, CHN1 (includes EG:1123), MT1X, RRM2, IER3, RAB31, ARHGDIB, C14ORF132, CTSB, TFRC, UBE2C, FN1, GBP1 (includes EG:2633), CD74, COL4A2, CCL5, TAP1, CORO2B, HLA-DPA1, CCL2, HLA-DRA, IGF1R, SNX10, SERPINA1, LAMB4, RPL13, MMP1 (includes EG:4312), IL11RA, PLAT, CD53, PKM2, PSMB9, CCNB1, TYROBP, DST, FGF14, ITGB2, PDZD2, SWAP70, S100A9, CIRBP, FCER1G, SORBS2, ID4, GZMB, MMP3, TRIM9, MELK, LYZ, PBK, BIRC5, FGFR3, CXCL14, LPL, SCEL, CDKN1C, DSP, GZMA, IL8, CXCL9, SPP1, COL4A1, XYLT1, TMEM204, SPARCL1, CD14, CCL19, IRF8, CCL18, DSC1, C2, TRA@, CDK2, FRZB, TFAP2B, ACOT7, TNFRSF12A, SOX9, KCNMA1, F5, S100A8, STAT1, HLA-DMA, CXCR4, C9ORF3, PRC1, CD36, PYGL, AZGP1, CD3D, HCLS1, CADM1, A2M, MMP9
Post-Translational Modification	1,1E-05-1,72E-04	IL8, SELL, FN1, SPP1, CNTN1, TSPAN7, CD2, TYROBP, PTN, CD36, CD48, APOC2, CCL5, TUSC3, FGFR3, ITGB2, SATB1, FCER1G, IGF1R, SERPINA1, STAT1, CDK2, MMP1 (includes EG:4312), UBE2C
Hematological Disease	1,52E-05-6,23E-04	SELL, FN1, CD2, KPNA2, PTTG1, C1QA, CCL5, CD74, BIRC5, CXCL10, FGFR3, CCL2, CXCL13, KCNMA1, F5, CXCL14, LPL, PTPRZ1, CFH, PLAT, IL11RA, IL8, CXCL9, COL4A1, SPP1, CXCR4, CD36, RRM2, HCLS1, CD3D, ITGB2, ABCA8, S100A9, SATB1, FCER1G, CD14, IRF8, GATA3, CDK2, C2, MMP9
Organismal Injury and Abnormalities	1,52E-05-1,06E-03	SELL, KRT6A, LHX2, IFI27, HSPB2, CXCL10, CCL2, LPL, HLA-DRA, SERPINA1, IFI6, STAT1, DSP, CXCL11, IL11RA, IL8, PSMB9, SPP1, CXCL9, OAS2, CXCR4, UPP1, COL17A1, CD36, ITGB2, S100A9, KLF5, CTSB, DSC1, MMP9, CDK2
Cell Cycle	5,02E-05-1,2E-03	KIF20A, TYMS, DLGAP5, PLAGL1, CCNB1, FN1, TNC, CKS2, PTTG1, GDF15, SSBP2, IER3, AURKA, BIRC5, NR2E1 (includes EG:7101), SOX9, STAT1, CDKN1C, NEDD4L, ZBTB16, CDK2, MMP9
Hypersensitivity Response	7,46E-05-1,19E-03	CXCL10, IL8, ITGB2, CXCL9, CD2, CCL2, CD48, CCL5, CXCL11
Nucleic Acid Metabolism	1,55E-04-1,55E-04	CXCL10, CXCL9, CXCL11
Small Molecule Biochemistry	1,55E-04-1,55E-04	CXCL10, CXCL9, CXCL11
Carbohydrate Metabolism	2,4E-04-2,4E-04	KRT14, CXCL10, IL8, TNC, SPP1, FN1, CD14
Organismal Development	2,54E-04-8,06E-04	IL8, COL4A1, FN1, MMP3, CXCR4, CD36, COL4A2, CITED1, TNFRSF12A, CXCL10, ITGB2, WARS, NR2E1 (includes EG:7101), CCL2, KLF5, CXCL14, CTSB, ECM1, MMP1 (includes EG:4312), MMP9, HEY1, PLAT
Cellular Assembly and Organization	2,68E-04-2,68E-04	SWAP70, CCL2, CCL5
Endocrine System Disorders	3,11E-04-3,11E-04	RGS1, COL4A1, SPP1, FN1, SERPINA3, CD74, A2M, C2
Metabolic Disease	3,11E-04-3,11E-04	RGS1, COL4A1, SPP1, FN1, SERPINA3, CD74, A2M, C2
Organismal Survival	3,79E-04-3,79E-04	S100A1, CXCL9, CNTN1, CD2, CD48, LYZ, CD74, TAP1, BIRC5, CXCL10, CCL2, HLA-DRA, LPL, CTSB, CD14, BCL2A1, STAT1, DSP, MMP9, CXCL11, PLAT
Embryonic Development	4,05E-04-4,05E-04	COL4A1, COL4A2
Nervous System Development and Function	4,05E-04-4,05E-04	FN1, CHL1
Visual System Development and Function	4,05E-04-4,05E-04	NR2E1 (includes EG:7101), CDKN1C
Cardiovascular Disease	4,22E-04-1,06E-03	MMP3, HSPB2, LPL, CD36, MMP1 (includes EG:4312), MMP9, DSP
Organismal Functions	4,94E-04-4,94E-04	GZMA, PTPRZ1, PLAT, GZMB
Connective Tissue Development and Function	6,23E-04-6,23E-04	FGFR3, SOX9, MMP9
Skeletal and Muscular System Development and Function	6,23E-04-1,2E-03	FGFR3, S100A1, SOX9, FN1, SERPINA3, A2M, MMP9, MMP1 (includes EG:4312)
Renal and Urological	1,06E-03-	CXCL10, IL8, CXCR4, CCL5

System Development and Function	1,06E-03	
Renal and Urological Disease	1,08E-03-1,08E-03	PKM2, FGFR3, TYMS, PRC1, RRM2, AURKA, MMP9, PLAT, UBE2C, BIRC5
Antimicrobial Response	1,2E-03-1,2E-03	GZMA, GZMB
Organ Morphology	1,2E-03-1,2E-03	S100A1, MMP1 (includes EG:4312)

Supplemental Table 2: The Functional Analysis according to Ingenuity's™ Knowledge Base identified the biological functions that were most significant to regulated genes in PM compared to MN comprising cancer, cellular growth and development.

Category	p-value	Molecules
Hair and Skin Development and Function	7,99E-26-1,4E-02	CSTA, KRT6A, KLK6, CTSL2, VEGFA, KLK5, SCEL, JUP, KRT1, DSP, KRT16, SELE, GJA1, CDSN, KRT10, KLF4, KLK7, CDH1, TGM1, SPINK5, LAMA3, DSC1, CST6, KRT15, ALOX12B, FN1, SPRR1A, ID1, DSG3, CDH3, KRT2, KIT, LOR, EGFR, KRT14, TIMP3, CALML5, IVL, TP63, KRT17, SPRR1B, COL17A1, LAMC2, KLK8, TYRP1, DHCR24, KRT5, BNC1, CRABP2, SFN
Organ Development	7,99E-26-1,23E-02	ALOX12B, FN1, SPRR1A, CTSL2, VEGFA, FGFR3, ALDH1A1, KLK5, KIT, KRT2, SCEL, DSC2, LOR, KRT1, DSP, EGFR, KRT14, KRT16, GJA1, CALML5, TP63, SPRR1B, KRT17, COL17A1, CDSN, KRT10, LAMC2, MET, HOPX, KLK7, CDH1, SPINK5, TF, DHCR24, KRT5, BNC1, CRABP2, LAMA3, CST6, SFN, KRT15
Dermatological Diseases and Conditions	3,73E-19-1,43E-02	KRT6A, FCER1A, KLK6, SERPINB2, CTSL2, VEGFA, SLURP1, CCL27, ZNF750, JUP, KRT1, DSP, KRT16, GJA1, SELE, SPP1, SERPINB3, CDSN, KRT10, DSG1, CDH1, SPINK5, TGM1, IL1RN, FERMT1, LAMA3, DSC1, ABCA12, ALOX12B, FN1, GJB3, HLA-DQA1, SLPI, DSG3, CD1A, KIT, KRT2, S100A8, LOR, MMP1 (includes EG:4312), EGFR, KRT14, SDC1, TP63, KRT6B, KRT17, PERP, COL17A1, TUBA4A, S100A12, LAMC2, TYRP1, S100A9, KRT5
Cancer	5,73E-16-1,21E-02	KRT6A, ASS1, KLK6, SERPINA3, RPS4Y1, SERPINB2, CTSL2, VEGFA, KLK5, MGP, PTGIS, SELE, IGH@, DCN, GSTM3 (includes EG:2947), KRT23, KRT10, S100A2, MET, KLK7, CDH1, SPINT2, ANK3, CA2, FN1, SLPI, AQP3, KLK11, DSG3, ID1, MT1E, CDH3, TRIM29, KLK10, MMP1 (includes EG:4312), EGFR, TACSTD2, PLOD2, KRT6B, KRT17, DST, DEFB1, S100A14, C10ORF116, LAMC2, SERPINB4, NOV, S100A9, DHCR24, KRT5, BNC1, SFN, CXADR, EYA1, QPCT (includes EG:25797), TRIM9, MBP, SCUBE2, FCER1A, LAD1, FGFR3, GPX3, ALDH1A1, CCL27, CXCL14, CFI, JUP, SERPINB5, KRT1, AIM1 (includes EG:202), KRT16, GJA1, SPP1, LCN2, SERPINB3, CAPG, ZNF185, TUSC3, AKR1C2, KLF4, IGFBP2, STC1, IL1RN, AKR1B10, LAMA3, DSC1, S100P, IFI27, CD1A, C7, KIT, S100A8, CD24, KRT14, KLK13, TIMP3, TP63, SDC1, TUBA4A, PERP, PPL, CPA4, KLK8, HOPX, CRABP2, KLF5
Reproductive System Disease	5,73E-16-4,17E-03	NELL1, KRT6A, TRIM9, MBP, ASS1, SCUBE2, LAD1, KLK6, VEGFA, FGFR3, CTSL2, GPX3, ALDH1A1, CXCL14, KLK5, CFI, MGP, SERPINB5, JUP, KRT1, AIM1 (includes EG:202), SELE, SPP1, GSTM3 (includes EG:2947), DCN, LCN2, KRT23, SERPINB3, AKR1C2, TUSC3, KLF4, S100A2, IGFBP2, MET, STC1, CDH1, KLK7, LAMA3, SPINT2, CCL18, S100P, ANK3, FN1, IFI27, SLPI, KLK11, ID1, MT1E, CDH3, C7, KIT, S100A8, CD24, MMP1 (includes EG:4312), KLK10, EGFR, TACSTD2, POF1B, TIMP3, TP63, KRT6B, KRT17, DST, TUBA4A, DEFB1, S100A14, KLK8, SERPINB4, HOPX, S100A9, DHCR24, KRT5, BNC1, CRABP2, SFN, EYA1, CXADR
Cellular Development	2,54E-13-1,43E-02	NELL1, CSTA, KRT6A, MBP, SERPINA3, SERPINB2, FGFR3, CTSL2, VEGFA, SLURP1, ALDH1A1, MGP, SERPINB7, SCEL, JUP, DSP, GJA1, SPP1, PKP3, DCN, LCN2, CAPG, KRT10, KLF4, IGFBP2, MET, STC1, CDH1, SPINK5, TGM1, IL1RN, LAMA3, CST6, DSC1, CA2, FN1, HLA-DQA1, SPRR1A, SYNM, ID1, KIT, S100A8, LOR, CD24, MMP1 (includes EG:4312), EGFR, TIMP3, IVL, SDC1, TP63, SPRR1B, TYRP1, HOPX, NOV, S100A9, CRABP2, KLF5, SFN, CXADR, EYA1
Genetic Disorder	1,38E-11-1,43E-02	NELL1, KRT6A, ASS1, CA12, KLK6, SERPINA3, EXPH5, VEGFA, SCNN1A, SLURP1, HAL, KLK5, MGP, SERPINB7, PTGIS, MALL, SELE, DCN, CPA3, KRT10, S100A2, DSG1, MET, KLK7, CDH1, TGM1, SPINT2, VSNL1, ANK3, CA2, FN1, HLA-DQA1, SLPI, ABLIM1, DSG3, KLK11, ID1, AQP3, HLA-DQB2, MT1E, CDH3, KRT2, CLIC3, TRIM29, MMP1 (includes EG:4312), KLK10, EGFR, TACSTD2, NMU, DSC3, POF1B, PLOD2, KRT6B, KRT17, DST, COL17A1, ELOVL4, DEFB1, LAMC2, S100A9, TF, DHCR24, KRT5, BNC1, ANXA3, EYA1, QPCT (includes EG:25797), TRIM9, SLC6A14, MBP, SCUBE2, FCER1A, LPPR4, MT1M, FGFR3, GPX3, ALDH1A1, ZNF750, CCL27, CXCL14, CFI, IMPA2, SCEL, SERPINB5, JUP, KRT1, DSC2, DSP, AIM1 (includes EG:202), KRT16, BBOX1, GJA1, SPP1, LCN2, SERPINB3, CDSN, CAPG, ZNF185, AKR1C2, TUSC3, IGFBP2, SPINK5, FERMT1, IL1RN, AKR1B10, LAMA3, DSC1, CCL18, ABCA12, ARG1, S100P, ALOX12B, GJB3, TUFT1, CDS1, CD1A, C7, KIT, S100A8, LOR, CD24, KRT14, TIMP3, TP63, SDC1, PERP, TUBA4A, S100A12, KLK8, TYRP1, HOPX, KLF5, RHCG
Cellular Movement	1,79E-08-1,43E-02	KRT6A, FCER1A, KLK6, SERPINA3, SERPINB2, CTSL2, VEGFA, CCL27, CXCL14, MGP, SERPINB5, JUP, KRT16, SELE, GJA1, SPP1, PKP3, DCN, LCN2, SERPINB3, KRT10, S100A2, KLF4, IGFBP2, STC1, MET, CDH1, IL1RN, LAMA3, SPINT2, CCL18, CST6, VSNL1, S100P, FN1, SLPI, SYNM, ID1, CDH3, KIT, S100A8, CD24, CALML3, MMP1 (includes EG:4312), NMU, EGFR, TIMP3, TP63, SDC1, PRSS3 (includes EG:5646), COL17A1, DEFB1, LRRC15, LAMC2, LYPD3, NOV, S100A9, KLF5
Cellular Growth and Proliferation	2,83E-08-1,43E-02	NELL1, MBP, FCER1A, KLK6, SERPINB2, CTSL2, FGFR3, VEGFA, SLURP1, ALDH1A1, CCL27, MGP, SERPINB7, SERPINB5, JUP, CLCA2 (includes EG:9635), KRT16, GJA1, SPP1, PKP3, DCN, LCN2, KRT10, FGFBP1, KLF4, IGFBP2, MET, STC1, CDH1, IL1RN, LAMA3, SPINT2, CST6, ARG1, S100P, FN1, SLPI, SYNM, ID1, DSG3, MT1E, KIT, KRT2, S100A8, CD24, EGFR, TACSTD2, KLK13, TIMP3, TP63, DEFB1, KLK8, TYRP1, NOV, S100A9, TF, DHCR24, BNC1, CRABP2, KLF5, SFN, CXADR
Respiratory Disease	4,28E-08-1,16E-02	CA2, FN1, CA12, KLK6, SLPI, RPS4Y1, SCNN1A, FGFR3, VEGFA, ID1, DSG3, KLK11, KLK5, MGP, IMPA2, KIT, SERPINB5, CD24, KLK10, EGFR, PTGIS, TIMP3, IVL, SELE, SPP1, TP63, KRT6B, LCN2, SERPINB3, TUBA4A, S100A12, AZGP1, KLK8, MET, CDH1, KLK7, TF, S100A9, IL1RN, KRT5, ANXA3, AKR1B10, LAMA3, ARG1, S100P
Cell-To-Cell Signaling and Interaction	1,1E-07-1,43E-02	MBP, FCER1A, KLK6, SERPINB2, CTSL2, VEGFA, SLURP1, CCL27, SERPINB5, JUP, KRT1, DSC2, DSP, CLCA2 (includes EG:9635), KRT16, SELE, GJA1, SPP1, DCN, LCN2, SERPINB3, CDSN, KLF4, IGFBP2, STC1, MET, CDH1, SPINK5, IL1RN, LAMA3, VSNL1, CST6, ANK3, FN1, HLA-DQA1, SLPI, ID1, DSG3, CD1A, CDH3, KRT2, KIT, S100A8, CD24, MMP1 (includes EG:4312), NMU, EGFR, DSC3, TIMP3, SDC1, TP63, COL17A1, PERP, S100A12, AZGP1, LAMC2, LYPD3, S100A9, PI3, CXADR

Tissue Development	1,1E-07-1,43E-02	NELL1, KRT6A, KLK6, SERPINB2, FGFR3, VEGFA, SLURP1, ALDH1A1, SERPINB5, JUP, DSC2, CLCA2 (includes EG:9635), KRT16, SELE, GJA1, SPP1, DCN, LCN2, CDSN, STC1, MET, CDH1, SPINK5, IL1RN, LAMA3, DSC1, VSNL1, CST6, CA2, FN1, SLPI, ID1, DSG3, CDH3, C7, KIT, S100A8, CD24, EGFR, DSC3, TIMP3, TP63, SDC1, KRT6B, KRT17, PERP, AZGP1, LAMC2, DHCR24, S100A9, KLF5, EYA1, CXADR
Endocrine System Disorders	1,39E-07-9,55E-03	CA2, SELE, FN1, SPP1, LCN2, CA12, SERPINA3, KLF4, IGFBP2, VEGFA, ID1, CDS1, TF, IL1RN, EYA1, EGFR
Metabolic Disease	1,39E-07-7,7E-04	CA2, SELE, FN1, SPP1, LCN2, CA12, SERPINA3, KLF4, IGFBP2, VEGFA, ID1, CDS1, TF, IL1RN
Connective Tissue Development and Function	1,63E-06-1,18E-02	NELL1, GJA1, FN1, SPP1, PKP3, DCN, VEGFA, STC1, FGFR3, MET, CDH1, IL1RN, CDH3, MGP, JUP, EGFR
Renal and Urological Disease	3,84E-06-1,21E-02	CA2, FN1, MBP, CA12, SERPINA3, VEGFA, FGFR3, AQP3, MT1E, CFI, KIT, JUP, AIM1 (includes EG:202), EGFR, TIMP3, SPP1, LCN2, TUBA4A, PPL, DEFB1, IGFBP2, MET, STC1, CDH1, IL1RN, VAMP8
Inflammatory Response	4,82E-06-1,28E-02	FN1, FCER1A, SERPINA3, SLPI, VEGFA, CTSL2, DSG3, CCL27, CXCL14, C7, S100A8, NMU, EGFR, SELE, GJA1, SDC1, SPP1, COL17A1, DEFB1, CAPG, S100A12, TYRP1, S100A9, TF, IL1RN, PI3, DSC1, CCL18
Neurological Disease	8,18E-06-1,43E-02	NELL1, KRT6A, MBP, SCUBE2, LPPR4, CA12, MT1M, SERPINA3, FGFR3, CTSL2, VEGFA, ALDH1A1, CCL27, MGP, IMPA2, SCEL, DSP, AIM1 (includes EG:202), PTGIS, KRT16, SELE, GJA1, BBOX1, SPP1, DCN, LCN2, CAPG, CDSN, TUSC3, AKR1C2, ZNF185, KRT10, IGFBP2, TGM1, IL1RN, FERMT1, LAMA3, VSNL1, DSC1, S100P, ARG1, ABCA12, ANK3, CA2, GJB3, HLA-DQA1, TUFT1, ABLIM1, HLA-DQB2, CDS1, MT1E, CD1A, C7, CLIC3, KIT, CD24, MMP1 (includes EG:4312), DSC3, EGFR, POF1B, KRT14, TIMP3, PLOD2, SDC1, TP63, KRT17, DST, PRSS3 (includes EG:5646), PERP, TUBA4A, DEFB1, S100A12, DHCR24, TF, S100A9, KLF5, ANXA3, EYA1
Gastrointestinal Disease	1,27E-05-1,18E-02	ANK3, CA2, FN1, TRIM9, KLK6, SERPINA3, FGFR3, CTSL2, VEGFA, AQP3, MT1E, KLK5, KIT, SERPINB5, CD24, KLK10, AIM1 (includes EG:202), EGFR, KRT14, KLK13, PLOD2, TIMP3, GJA1, SDC1, SPP1, TP63, LCN2, TUBA4A, CAPG, KRT10, AKR1C2, KLF4, CPA4, C10ORF116, MET, CDH1, IL1RN, CRABP2, LAMA3, SFN, QPCT (includes EG:25797)
Organismal Injury and Abnormalities	1,52E-05-1,06E-02	CA2, NELL1, KRT6A, IFI27, CA12, SLPI, FGFR3, VEGFA, CTSL2, SCNN1A, DSG3, MT1E, KIT, DSP, MMP1 (includes EG:4312), EGFR, NMU, PTGIS, PLOD2, SELE, GJA1, SPP1, PRSS3 (includes EG:5646), COL17A1, TUBA4A, SERPINB3, KRT10, STC1, HOPX, S100A9, IL1RN, KLF5, DSC1, ARG1
Cell Morphology	1,56E-05-1,43E-02	NELL1, KRT6A, FN1, KLK6, SERPINA3, SYNM, VEGFA, ID1, MGP, KRT2, SERPINB5, CD24, CALML3, EGFR, KRT16, TIMP3, SELE, GJA1, SPP1, SDC1, TP63, KRT17, DCN, LCN2, CAPG, KLF4, IGFBP2, STC1, MET, CDH1, SPINK5, IL1RN, BNC1, KLF5, LAMA3, ARG1
Immunological Disease	2,42E-05-1,43E-02	SPP1, FN1, MBP, FCER1A, COL17A1, HLA-DQA1, DSG1, VEGFA, FGFR3, DSG3, SPINK5, S100A9, IL1RN, KIT, CD24, CXADR
Skeletal and Muscular System Development and Function	2,71E-05-1,18E-02	NELL1, GJA1, SDC1, FN1, SPP1, DCN, SERPINA3, KLF4, MET, CTSL2, STC1, FGFR3, VEGFA, NOV, IL1RN, KLF5, MGP, KIT, SERPINB5, CXADR, MMP1 (includes EG:4312), ARG1, EGFR
Hematological System Development and Function	2,81E-05-1,2E-02	FN1, MBP, FCER1A, SERPINA3, SLPI, CTSL2, VEGFA, CCL27, CDH3, CXCL14, C7, KIT, S100A8, NMU, EGFR, TIMP3, GJA1, SELE, SPP1, LCN2, PRSS3 (includes EG:5646), COL17A1, DEFB1, CAPG, KRT10, STC1, TF, S100A9, IL1RN, PI3, CCL18, DSC1
Immune Cell Trafficking	2,81E-05-1,2E-02	FN1, FCER1A, SERPINA3, SLPI, VEGFA, CTSL2, CCL27, CDH3, CXCL14, C7, KIT, S100A8, CD24, NMU, EGFR, TIMP3, SELE, SPP1, SDC1, PRSS3 (includes EG:5646), SERPINB3, COL17A1, DEFB1, KRT10, STC1, S100A9, IL1RN, DSC1, CCL18
Organismal Functions	3,81E-05-4,11E-03	MET, VEGFA, HOPX, GJA1, SPP1, FN1, IL1RN, SLPI, SERPINB2
Inflammatory Disease	4,7E-05-7,5E-03	VEGFA, CA2, SPP1, S100A9, IL1RN, CA12, S100A8, S100A12, SERPINB2
Nutritional Disease	4,7E-05-4,7E-05	SCNN1A, DSG3, SPINK5
Cardiovascular System Development and Function	6,06E-05-1,4E-02	PTGIS, TIMP3, SELE, GJA1, SPP1, FN1, DCN, KLF4, VEGFA, MET, CTSL2, STC1, SLURP1, ID1, S100A9, KLF5, KIT, SERPINB5, KRT1, CXADR, MMP1 (includes EG:4312), EGFR
Ophthalmic Disease	8,11E-05-8,95E-03	CA2, SELE, DCN, ELOVL4, CA12, TUBA4A, VEGFA, FGFR3, TYRP1, TF, IL1RN, KIT, TACSTD2
Tumor Morphology	9,35E-05-1,43E-02	SELE, FN1, DCN, PERP, LRRC15, IGFBP2, SERPINB2, CTSL2, VEGFA, CDH1, NOV, IL1RN, JUP, SERPINB5, MMP1 (includes EG:4312), EGFR
Cell Death	1,73E-04-1,43E-02	CSTA, NELL1, MBP, FCER1A, SERPINA3, SERPINB2, VEGFA, CTSL2, FGFR3, ALDH1A1, CCL27, CFI, MGP, JUP, SERPINB5, DSP, CLCA2 (includes EG:9635), PTGIS, GJA1, SPP1, DCN, LCN2, SERPINB3, KRT10, KLF4, IGFBP2, DSG1, STC1, MET, CDH1, TGM1, IL1RN, S100P, ARG1, RAB25, FN1, SPRR1A, ID1, DSG3, MT1E, C7, KIT, S100A8, CD24, MMP1 (includes EG:4312), EGFR, TIMP3, SDC1, TP63, PERP, DEFB1, KLK8, SULT2B1, SERPINB4, TF, DHCR24, S100A9, KLF5, CRABP2, SFN, EYA1
Cardiovascular Disease	2,53E-04-1,43E-02	PTGIS, CA2, SELE, GJA1, KRT6A, LCN2, CA12, S100A12, SLPI, CTSL2, VEGFA, SCNN1A, S100A9, IMPA2, SERPINB5, JUP, DSC2, VSNL1, DSP, AIM1 (includes EG:202), S100P
Cellular Compromise	2,53E-04-3,09E-03	TYRP1, SELE, GJA1, SPP1, KRT6A, MT1E, IL1RN, PI3, EGFR
Connective Tissue Disorders	2,56E-04-2,75E-03	VEGFA, SPP1, S100A9, IL1RN, S100A8, S100A12, SERPINB2

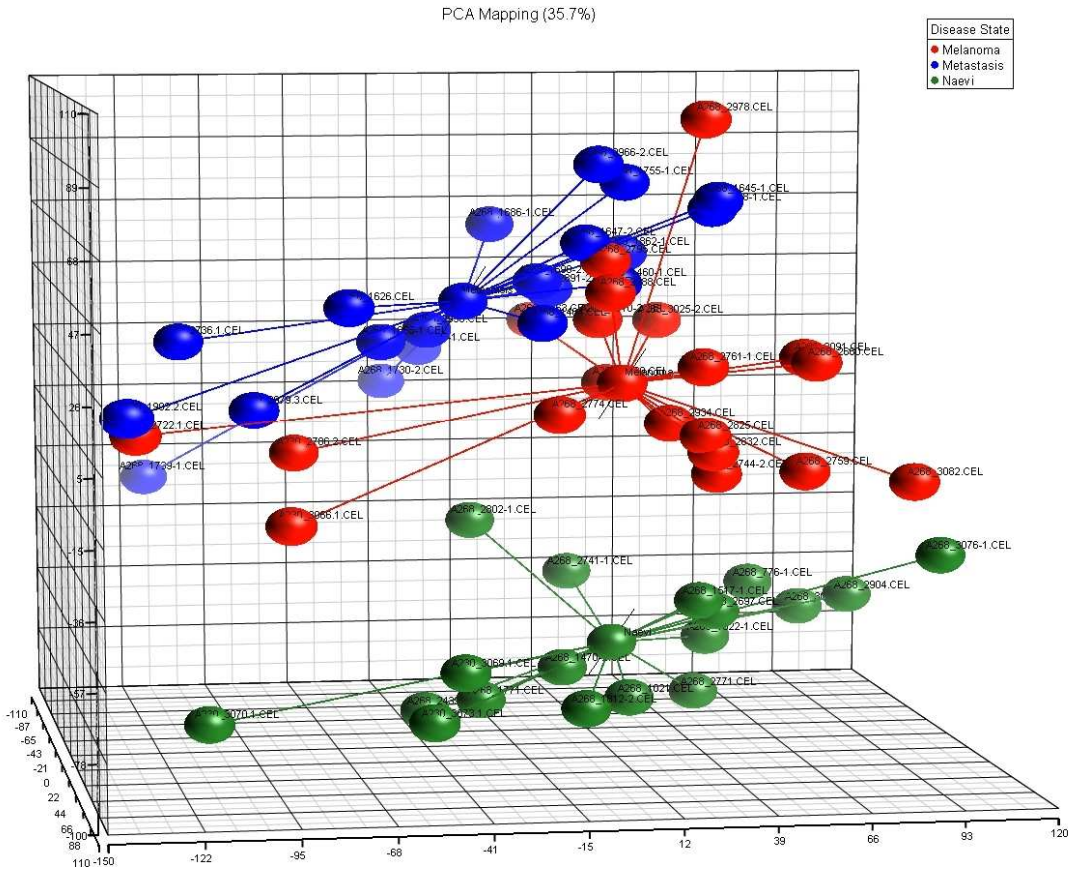
Cell Cycle	3,75E-04-1,43E-02	VEGFA, ID1, CDH1, SPP1, FN1, TF, KIT, SERPINB5, SFN, KLF4, EGFR
Carbohydrate Metabolism	4,72E-04-8,42E-03	KRT14, VEGFA, CDH1, SPP1, FN1, SLPI
Infectious Disease	8,37E-04-1,43E-02	FN1, S100A9, PI3, LCN2, IMPA2, S100A12, SLPI, RPS4Y1, CXADR, CD24, S100P
Cellular Assembly and Organization	8,51E-04-1,43E-02	GJA1, KRT6A, FN1, SPP1, KRT17, LAMC2, VEGFA, MET, CDH1, CCL27, MGP, LAMA3, JUP, DSP, EGFR
Cellular Function and Maintenance	8,51E-04-1,43E-02	VEGFA, CDH1, KRT6A, IL1RN, KRT17, MBP, LAMA3, FCER1A, VAMP8, DSC2, LAMC2
Embryonic Development	8,51E-04-1,31E-02	TIMP3, GJA1, KRT6A, FN1, TP63, KRT6B, LCN2, KLK6, MET, VEGFA, FGFR3, SLURP1, ALDH1A1, MGP, SERPINB5, EYA1, EGFR
Organ Morphology	8,51E-04-8,5E-03	KRT16, GJA1, FN1, TP63, KRT10, CTSL2, TYRP1, VEGFA, CDH1, TGM1, ALDH1A1, DHCR24, IL1RN, DSC2, DSC1, MMP1 (includes EG:4312), DSP, EGFR
Post-Translational Modification	8,51E-04-9,4E-03	FGFR3, VEGFA, GPX3, TP63, ALDH1A1, TGM1, FCER1A, KIT, CD24, EGFR
Protein Folding	8,51E-04-8,51E-04	VEGFA, TGM1
Reproductive System Development and Function	8,51E-04-1,43E-02	VEGFA, SELE, GJA1, CDH1, TP63, ALDH1A1, TF, KLF5, KIT, DSC2, CLCA2 (includes EG:9635)
Tissue Morphology	8,51E-04-8,43E-03	GJA1, SELE, SPP1, FCER1A, KLF4, MET, CTSL2, VEGFA, STC1, TF, S100A9, PI3, S100A8, SFN, MMP1 (includes EG:4312), ARG1
Organismal Development	8,98E-04-8,42E-03	MET, VEGFA, STC1, TIMP3, SLURP1, FN1, KLF5, SERPINB5, MMP1 (includes EG:4312)
Hepatic System Disease	1,68E-03-1,68E-03	MT1E, IL1RN
Renal and Urological System Development and Function	1,68E-03-1,43E-02	MET, TIMP3, CDH1, FN1, TP63, ALDH1A1, LCN2, KLK6
Hematological Disease	2,24E-03-1,43E-02	VEGFA, PLOD2, SELE, SPP1, FN1, S100A9, IL1RN, KIT, CXADR
Skeletal and Muscular Disorders	2,51E-03-9,63E-03	GJA1, SPP1, ASS1, LCN2, TUBA4A, S100A12, RPS4Y1, FGFR3, S100A9, CRABP2, IMPA2, KIT, S100A8, VSNL1, AIM1 (includes EG:202), S100P
Cell Signaling	2,77E-03-7,51E-03	ASS1, FCER1A, VAMP8, ARG1
Drug Metabolism	2,77E-03-2,77E-03	PTGIS, VEGFA
Lipid Metabolism	2,77E-03-1,08E-02	VEGFA, PTGIS, ALOX12B, SPP1, S100A9, FCER1A, S100A8, AKR1C2, NMU
Molecular Transport	2,77E-03-1,18E-02	SPP1, TF, MT1E, S100A9, SLC6A14, FCER1A, S100A8, VAMP8, ARG1, NMU
Small Molecule Biochemistry	2,77E-03-1,18E-02	PTGIS, ALOX12B, SPP1, SLC6A14, FCER1A, AKR1C2, FGFR3, VEGFA, CDH1, ALDH1A1, S100A9, AKR1B10, KIT, S100A8, CD24, EGFR, NMU, ARG1
Lymphoid Tissue Structure and Development	2,83E-03-6,44E-03	PTGIS, SELE, GJA1, S100A9, TF, KLF5, PI3, FCER1A, S100A8, KLF4
Visual System Development and Function	4,11E-03-4,11E-03	MET, VEGFA
Hematopoiesis	4,44E-03-1,18E-02	VEGFA, SELE, IL1RN, MBP, LCN2, KIT, EGFR
Infection Mechanism	5,7E-03-5,7E-03	PI3, CXADR
Cell-mediated Immune Response	7,05E-03-1,18E-02	CTSL2, SELE, SPP1, FN1, CCL27, IL1RN, MBP, DEFB1, CCL18
Amino Acid Metabolism	7,51E-03-1,18E-02	FGFR3, ASS1, SLC6A14, FCER1A, KIT, CD24, EGFR, ARG1
Protein Degradation	7,51E-03-7,51E-03	TIMP3, KLK6
Respiratory System Development and Function	8,42E-03-8,42E-03	FGFR3, VEGFA, HOPX
Developmental Disorder	9,4E-03-9,55E-03	FGFR3, VEGFA, EYA1, EGFR
Protein Synthesis	9,4E-03-9,4E-03	GPX3, TP63, ALDH1A1
Endocrine System Development and Function	9,55E-03-9,55E-03	SPP1, NMU
Antigen Presentation	1,18E-02-1,18E-02	FN1, CAPG

Supplemental Table 3: The Functional Analysis according to Ingenuity's™ Knowledge Base identified the biological functions that were most significant to regulated genes in MM compared to PM comprising cancer, cellular movement, cellular growth and proliferation.

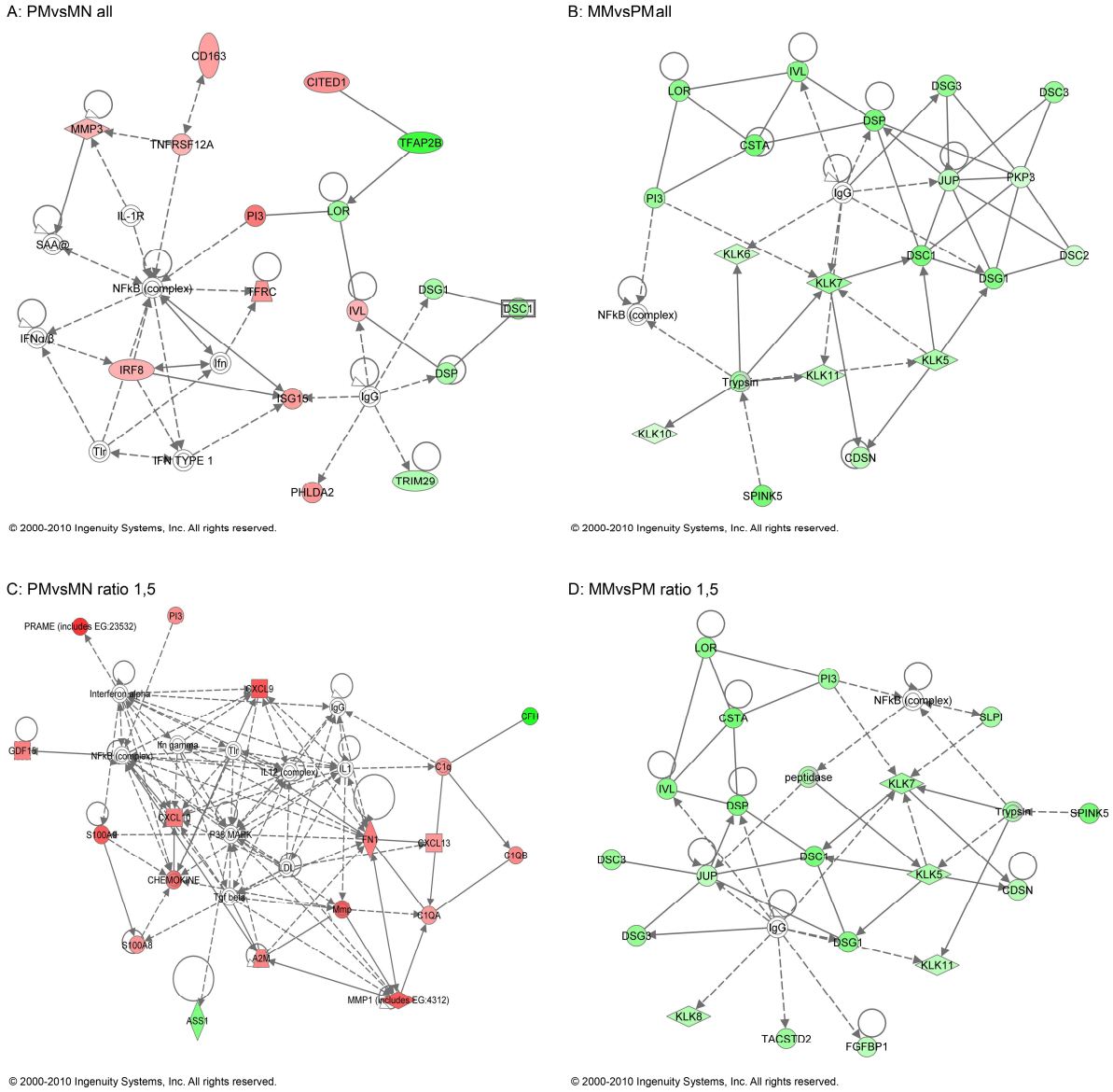
GDF 15	MN			PM			MM		
	A.M.	T.V.	mean	A.M.	T.V.	mean	A.M.	T.V.	mean
- negative	48	45	46,5	7	5	6	17	15	16
(+) weakly positive	45	51	48	2	3	2,5	3	4	3,5
+ positive	32	28	30	26	23	24,5	31	25	28
++ strongly positive	2	3	2,5	27	28	27,5	26	31	28,5
+++ very strongly positive	0	0	0	11	14	12,5	12	14	13

MMP 1	MN			PM			MM		
	A.M.	T.V.	mean	A.M.	T.V.	mean	A.M.	T.V.	mean
- negative	1	5	3	0	0	0	2	5	3,5
(+) weakly positive	14	22	18	1	0	0,5	11	14	12,5
+ positive	51	47	49	14	12	13	27	33	30
++ strongly positive	54	48	51	44	50	47	32	25	28,5
+++ very strongly positive	6	4	5	17	14	15,5	19	14	16,5

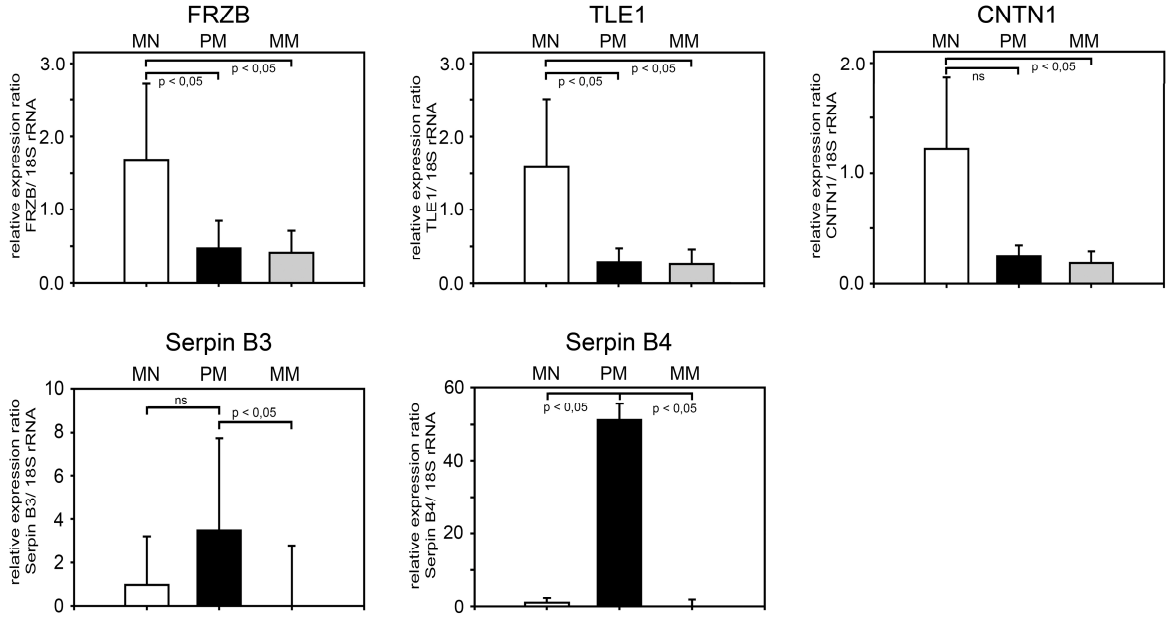
Supplemental Table 4: Two independent investigators (A.M., T.V.) evaluated immunostaining of tissue specimens based on a 5-step scoring system.



Supplemental Figure 1: Principal component analysis displays spatial separation of melanocytic nevi (MN), primary melanomas (PM), and melanoma metastases (MM). Results of PCA are shown in the three-dimensional contribution scores, which discriminate the three entities.



Supplemental Figure 2A/B/C/D: Ingenuity Network analysis of all significantly regulated genes in PM compared to MN (Figure A), MM compared to PM (Figure B). Analysis of genes with a minimum log ratio of 1.5 in PM compared to MN (Figure C), MM compared to PM (Figure D). Green symbols show down-regulation, red symbols show up-regulation in PM compared to MN (Figure A/ C) and in MM compared to PM (Figure B/ D).



Supplemental Figure 3: Confirmation of differential gene expression by quantitative real-time RT-PCR (ns= not significant).

Deutsche Zusammenfassung der Promotionsarbeit mit dem publizierten Titel: **“Identification of new genes associated with melanoma”**

Identifizierung neuer melanomassoziierter Gene

Andreas Mauerer

Mit der vorliegenden Arbeit sollen neue Erkenntnisse über die Genexpressionsmuster und Signalkaskaden des malignen Melanoms gewonnen werden. Während Melanom-Patienten mit einer Tumordicke von unter 1 mm (Stadium I) eine gute Prognose haben, sinkt die Fünf-jahresüberlebensrate bei Vorliegen von Fernmetastasen (Stadium IV) unter 10 % [1]. Auf eine Standardchemotherapie sprechen nur zwischen 5,3 und 23% der Patienten an [2, 3]. Wegen dieser geringen Ansprechrate werden neue Therapieansätze verfolgt, die auf der Blockade molekularer Prozesse in der Signaltransduktion der Zelle beruhen. Die Selbstregulation der Melanomzelle wird von einer Vielzahl an Genen gesteuert. Deshalb ist es für neue diagnostische und therapeutische Ansätze wichtig, bevorzugt das Gesamtexpressionsmuster zu betrachten anstatt nur ein Einzelgen zu verfolgen [4]. Seit der Entwicklung der Mikroarray-Technologie ist es möglich die Expression einer Vielzahl von Genen in einer Gewebeprobe zu untersuchen. Mit einer geeigneten Software können Netzwerke von Signalkaskaden in den einzelnen Proben analysiert und verglichen werden.

In dieser Arbeit wurden humane Gewebeproben von 18 melanozytären Nävuszellnävi (MN), 20 Melanomen (PM) und 20 Melanommetastasen (MM) aus der Abteilung für Dermatologie der Universität Regensburg verwendet. Ein Teil des entfernten Patientengewebes wurde nach der Gewinnung kryokonserviert. Nach Abschluss der Diagnosestellung wurde mittels Mikrodissektion Gewebe zur weiteren Untersuchung isoliert. Anschließend erfolgte die Isolierung der RNA und Überschreibung in zweisträngige cDNA und Biotin markierte cRNA. Nach deren Fragmentierung erfolgte die Hybridisierung auf Mikroarrays (Affymetrix Human Genome U133A 2.0 GeneChip®; Affymetrix, Santa Clara, USA). Zur Analyse und statistischen Untersuchung der gewonnen CEL Files wurde Chipinspector Version 1.3 (Genomatix Software GmbH, München, Germany) verwendet [5]. Mit Ingenuity^{TM} Pathways

Analysis (www.ingenuity.com, Ingenuity™ Systems, Mountain View, USA) [6] wurden funktionelle Verbindungen der signifikant regulierten Gene, Netzwerke und eingebundene Signalkaskaden aufgedeckt. Eine Hauptkomponentenanalyse erlaubte die dreidimensionale Darstellung der Einzelproben in Abhängigkeit von ihrem Expressionsmuster (Partek Genomic Suite 6.4 ,Partek Inc., St. Louis, USA).

Zur Validierung der Mikroarray Daten wurden zusätzlich quantitative Echtzeit-PCR (QPCR) Untersuchungen durchgeführt. Hierfür wurde RNA von fünf repräsentativen MN, von fünf PM und von fünf MM isoliert und in cDNA (SuperScript II, Invitrogen, Carlsbad, USA) übersetzt. Die Untersuchung erfolgte in dreifacher Ausführung mit Hilfe der kommerziell erhältlichen TaqMan™-Assays (Applied Biosystem, Foster City, USA) und individueller Primer (Apara Bioscience, Denzlingen, Germany).

Um die Genprodukte von GDF15 und MMP1 nachzuweisen, führten wir Tissue-Mikroarrays (TMA) durch [7]. Diese enthielten Gewebezylinder von 127 MN, 73 PM, und 89 MM auf einem Paraffinblock. Anhand von Standardprotokollen erfolgte eine Inkubierung mit polyklonalen anti-GDF15 Antikörpern (Abcam, Cambridge, UK) und monoklonalen anti-MMP1 Antikörpern (Millipore Corporation, Billerica, USA); danach Färbung mit Hilfe von biotinylierten Sekundärantikörpern (Zytochem Plus HRP Broad Spectrum Kit, Zytomed Systems, Berlin, Germany). Die Auswertung erfolgte durch zwei unabhängige Untersucher (A.M., T.V.) anhand eines fünfstufigen Bewertungssystems (0 bis 4+). Um die Überlebenszeit mit niedrigen und hohen Expressiongraden der Gene Serpin B3 und Serpin B4 zu vergleichen, verwendeten wir SPSS V.18.0 (SPSS Inc., Chicago, USA). Ein p-Wert <0.05 wurde als signifikant gewertet [8].

Bei der Auswertung der CEL Files wurden die Gruppe der PM mit der Gruppe der MN und die Gruppe der MM mit der Gruppe der PM verglichen. Die Werte mussten sich hierbei um den Faktor zwei unterscheiden, um als signifikant zu gelten. Chipinspector identifizierte für die Gruppe der PM im Vergleich mit der Gruppe der MN 167 Gene, die vermehrt, und 117 Gene, die vermindert exprimiert wurden. Beim Vergleich der Gruppe der MM mit der Gruppe der PM ergaben sich 26 vermehrt und 163 vermindert exprimierte Gene.

Beim Vergleich der Ergebnisse mit bereits publizierten Daten zeigten sich große Übereinstimmungen. Erhöhte Expressionswerte bei Melanomen im Vergleich mit melanozytären Nävi sind bekannt für PRAME, SSP1 [9, 10], CXCL9, PHACTR1, CITED-1, BCL2A1 [9, 11] S100A9, MMP1, FN1 [12], NNMT, SERPIN A3 [9], MCAM [13], ISG15 [14], CDK-2, und CDK-4 [15], GDF15 [9, 11, 16] und Hey1 [11, 12]. Erniedrigte Werte sind für CIRBP,

FEZ1, PPP1R3C, LDOC1, TRPM1 [12], Desmoglein [13], KRT-15 [9], FABP7 [16], p57KIP2 und CDKN1 [17] beschrieben.

Für die Gruppe der Melanommetastasen im Vergleich mit Melanomen ergab die Literaturrecherche ebenfalls erhöhte Expressionswerte für VEGFA [18, 19], FN1 [20, 21], IGFBP2 [22], SPP1, MAGEA12, c-MET [11, 21, 23], STC1, und PLOD2 [21] sowie verminderte Werte für Serpin B5 [24], SPRR1A, KRT 16/17/6B, CD 24, LOR, DSC1 [23], KRT 1/14/6A/5, CXCL14 und SPINT2 [21].

Wir nahmen an, dass die drei histologisch unterschiedlichen Gruppen anhand ihres Transkriptoms klassifiziert werden können und untersuchten dies mit Hilfe der Hauptkomponentenanalyse. Hierbei wurden die 58 Patientenproben anhand ihres Expressionsmusters räumlich dargestellt. Tatsächlich ergab sich in der dreidimensionalen Darstellung eine klare räumliche Trennung der drei Entitäten.

Um die Funktion der transkribierten Gene und deren Verbindungen untereinander zu analysieren nutzten wir die Datenbank der Ingenuity™ Software. Bei PM im Vergleich mit MN waren insbesondere die Gene exprimiert, die für Tumoren, dermatologische Erkrankungen, Zellwachstum, Zellwanderung und Entzündungsreaktionen eine Rolle spielen. Darüberhinaus konnten mit Hilfe des Ingenuity Network Algorithm™ 15 funktionelle Gennetzwerke erstellt werden. Darunter waren Gene, die in wichtige Zellfunktionen und in Signalkaskaden des malignen Melanoms involviert sind, insbesondere in die Apoptose, die Kontrolle der G1/S und G2/M Phasen, den Notch-, den MAP-Kinase-, den WNT/beta Catenin- und Integrin-Signalweg [25, 26]. Die beim Vergleich der MM mit den PM signifikant regulierten Transkripte sind laut Ingenuity™ Datenbank beteiligt an Haar und Hautentwicklung, dermatologischen Erkrankungen, Tumoren, Zellwachstum, Zellwanderung und Entzündungsreaktionen. Auch hier konnten wichtige Signalwege identifiziert werden, unter anderen VEGF-, PI3/AKT-, WNT/beta Catenin- und Integrin-Signalwege.

Um bisher noch nicht für das Melanom beschriebene Gene zu identifizieren, führten wir eine Ingenuity™ Analyse durch, bei der nur diejenigen differentiell exprimierten Transkripte einbezogen wurden, die eine minimale log- Ratio von 1,5 aufwiesen. Basierend auf intensiven Gene-Ontology Recherchen erwarteten wir insbesondere Gene, die in die bedeutenden Melanom-Signalwege MAP-Kinase-, Notch- und Wnt-Signalweg involviert sind. Hierbei identifizierten wir Contactin1 (CNTN1), ein Adhäsionsmolekül, das in den Notch- Signalweg eingebunden ist und bei PM im Vergleich mit MN geringer exprimiert war. Frizzled-related Protein (FRZB) und transducin-like enhancer of split 1 (TLE1) sind in den Wnt-Signalweg eingebunden und waren bei PM im Vergleich mit MN geringer exprimiert. Die Serpin

Peptidase Inhibitoren Serpin B3 und B4 waren bei PM im Vergleich mit MN sehr stark exprimiert und sind assoziiert mit dem MAP-Kinase Weg [27]. Zudem konnten wir die kürzlich beschriebene verstärkte Expression des growth differentiation factor 15 (GDF15) in PM [9, 11, 12] verifizieren.

Diese Beobachtung validierten wir mit Hilfe der Echtzeit-PCR Methode. Die von MN über PM bis hin zu MM abnehmenden Expressionswerte für CNTN1, FRZB und TLE1 wurden weitgehend mit hoher statistischer Signifikanz bestätigt. Auch die hohen Serpin B4 Expressionswerte bei PM verglichen mit MN und MM konnten reproduziert werden. Für Serpin B3 fanden wir signifikant erhöhte Werte bei PM verglichen mit MM und einen Trend in Richtung erhöhter Werte bei PM verglichen mit MN.

GDF15, ein potenzieller Marker mit interessanter Biologie, wurde exemplarisch ausgewählt, um unsere auf transkribierten Genen basierenden Daten auf Proteinebene zu überprüfen. Hierfür wählten wir Tissue-Mikroarrays (TMA) mit mehr als 280 humanen Gewebeproben. Als Kontrolle verwendeten wir MMP1, deren Genregulation bereits bekannt ist. Die immunhistochemischen Färbungen wurden anhand eines fünfstufigen Bewertungssystems (0 bis 4+) kategorisiert und zeigten hohe GDF15 Werte bei PM und MM, während das GDF15 Protein bei MN kaum nachweisbar war. Diese Beobachtungen stimmten mit den Werten des GeneChips® überein. Interessanterweise war die progressionsfreie Überlebenszeit der Melanom Patienten mit niedrigen GDF15 Protein Werten (0 bis 2+) signifikant höher als die der Patienten mit hohen GDF15 Werten (3+ bis 4+; p=0.037). Übereinstimmend mit früheren Berichten über Metalloproteinasen [28, 29] beobachteten wir hohe Werte für MMP1 bei PM und signifikant niedrigere Werte bei MM und MN. Beim Vergleich der Färbeintensität mit der Zeit des progressionsfreien Überlebens zeigte sich für MMP1 kein signifikanter Unterschied.

Wie bereits oben erwähnt, findet man in praktisch jeder Melanomzelle Veränderungen im MAP-Kinase-Weg, die zu einer Aktivierung dieses Signalwegs führen [30]. Seit der Entdeckung aktivierender Mutationen des BRAF Proteins beim Melanom [31-33] stand der MAP-Kinase-Weg im Mittelpunkt des Forschungsinteresses. Auch in unseren Daten fanden wir differentiell exprimierte Gene mit Bezug zu MAP-Kinase Signalen. So waren STAT1 und SPP1 bei PM verglichen mit MN verstärkt exprimiert, während PPP1R3C vermindert exprimiert wurde. Mitglieder der STAT-Familie werden als Antwort auf Zytokine und Wachstumsfaktoren phosphoryliert und können daraufhin dimerisieren und am Zellkern als Transkriptionsfaktoren agieren. Wie auch in früheren Studien gezeigt wurde, wird SPP1 bei

PM und MM sehr stark exprimiert [9, 21, 34]. Dagegen ist relativ wenig über PPP1R3C bei Tumoren bekannt. PPP1R3C werden Tumor-Suppressorfunktionen zugeschrieben, da bei Melanomen verglichen mit Melanozyten eine Promotor-Hypermethylierung und eine geringere mRNA Expression beobachtet wurden [35]. Als neue progressionsassoziierte Marker mit Bezug zu MAP-Kinase Signalen konnten wir zwei Serpin-Peptidase-Inhibitoren, Serpin B3 und Serpin B4, identifizieren. Beide waren bei PM verglichen mit MN stark hochreguliert und bei Metastasen herunterreguliert. Kürzlich wurde gezeigt, dass Serpin B3 ein spezifischer endogener Inhibitor der c-Jun-NH²-Terminal Kinase-1 (JNK1/MAPK8) ist und UV-exponierte Keratinozyten vor apoptotischem Zelltod nach Sonnenexposition bewahrt [36]. Über die Rolle von Serpin B3 und B4 beim Melanom ist wenig bekannt. Bei Plattenepithelkarzinomen der Zervix, der Lunge, des Kopf-Hals-Bereichs wird Serpin B3 bereits als Tumormarker verwendet [37, 38]. Serpin B4 könnte ein allgemeiner Marker für Tumorinvasion und Metastasierung sein. Eine Inaktivierung durch Antisense cDNA führt bei humanen Zervixkarzinom-Zellkulturen zu einem Abfall der E-Cadherin-Expression, was allgemein einen bekannten Schritt für den Verlust der Zell-Zell-Adhäsion darstellt. [39]. Da auch Melanomzellen durch Herunterregulation von E-Cadherin der Kerationozytenkontrolle entkommen können [13], nehmen wir an, dass Serpine eine wichtige Rolle in der Melanomprogression spielen. Diese Annahme wird durch die Beobachtung bekräftigt, dass ein weiteres Mitglied der Familie der Serpine, Serpin B5 (Maspin), bei MM vermindert exprimiert wurde. Der Verlust von Serpin B5 gilt als Marker für Invasion und Migration bei anderen Tumorentitäten wie Brust-, Prostata- und Pankreaskarzinomen [40].

Ein weiteres signifikant reguliertes Gen in unseren Daten mit Verbindungen zum MAP-Kinase Signalweg ist GDF15, ein Mitglied der TGF-ß Superfamilie [41]. Wir fanden deutlich erhöhte Expressionswerte für PM und MM verglichen mit MN; gleichzeitig konnten wir nach Auswertung unserer Patientendaten feststellen, dass erhöhte GDF15 Werte mit einer verkürzten progressionsfreien Überlebenszeit assoziiert waren. Wie Boyle et al. bereits feststellen konnten, kann die Tumorigenität von unterschiedlichen Melanom-Zelllinien in einem Maus-Xenograft Model durch Inhibierung von GDF15 reduziert werden [42]. Erhöhte GDF15 Werte bei PM und MM wurden auch von Talantov et al. beschrieben, die zudem GDF15 als geeigneten Marker zur Differenzierung von Melanomen und Nävi vorschlugen [11]. Da GDF15 in weitere Tumor-Signalwege eingebunden ist, wie z. B. p53 [43], MITF [44], und PI3K/AKT-Signalwege [42, 45, 46], könnte es eine Schlüsselposition für die Entwicklung von Melanommetastasen mit schlechter Prognose und Überlebenszeit besitzen [47].

Beim Melanom wurden zudem aberrante Aktivierungen des Wnt-Signalwegs beobachtet [48]. Mit FRZB und TLE1 wurden in unseren Daten zwei wichtige Bausteine des Wnt-Signalwegs bei PM verglichen mit MN geringer exprimiert. FRZB (sFRP3) gehört zur Familie der secreted Frizzled-related Proteine, deren Mitglieder eine Ligand-Rezeptor Interaktion durch die Bindung extraxellulärer Wnt-Liganden verhindern [49, 50]. Da FRZB bei Pleura-mesotheliomen [51] und Prostatakarzinomen [52] geringer exprimiert wird, wurde eine Tumor-Suppressorfunktion vermutet.

TLE1, ein Corepressor, ist Mitglied der Groucho/TLE/Grg Familie und an einigen Signalwegen beteiligt [53, 54]. Im Wnt-Signalweg interagiert es mit wichtigen Trans-skriptionsfaktoren, unter anderen mit TCF/LEF-1 [55]. Es wird angenommen, dass eine Inaktivierung von TLE1 an der Entwicklung hämatoonkologischer Erkrankungen beteiligt ist, da entscheidende Differenzierungswege und wachstumshemmende Signalwege unterbrochen werden [56]. Im Notch-Signalweg fungiert TLE1 als Corepressor von HES1, einem Gen, das bei einigen humanen Tumorerkrankungen aktiviert ist und Tumorzellen erlaubt, der Differenzierung und der irreversiblen Ruhephase zu entkommen [50, 57]. Auch CNTN1 ist am Notch-Signalweg beteiligt. Es ist ein Mitglied der Immunglobulin-Superfamilie und ein neuronales Membranprotein, das als Adhäsionsmolekül und funktioneller Ligand von Notch wirkt. Es ist unter anderem an der Oligodendrozytenreifung beteiligt [58]. Abhängig vom Gewebe können Notch-Signalwege durch die Beeinflussung von Tumorzelldifferenzierung, Proliferation und Apoptose sowohl tumorinitiierende als auch tumorsupprimierende Effekte auslösen. [59, 60]. Bei Melanomen scheint eine Aktivierung von Notch-Signalwegen wichtig für die gesamte Tumorprogression. So führt eine verstärkte Expression von Nic, der aktiven Form von Notch, in Melanozyten zu einer malignen Transformation, während eine Akti-vierung von Notch1 bei Melanomzellen eher einen metastatischen Phänotyp bewirkt [61, 62].

Die Studie konnte zeigen, dass sich Primärtumoren und Metastasen des Melanoms durch unterschiedliche Genexpressionsmuster unterscheiden, insbesondere auch im Vergleich mit gutartigen Melanozyten. Die differentiell regulierten Gene spiegeln die Aktivierung und Inaktivierung wichtiger Tumor-Signalwege wider. Hierbei fanden sich die für Melanome bereits beschriebenen MAP-Kinase-, Wnt- und Notch- Signalwege mit bisher noch nicht beteiligten Genen. Um daraus diagnostischen und therapeutischen Nutzen ziehen zu können, bedarf es weiterer zukünftiger Untersuchungen.

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